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TOTAL SYNTHESIS OF d, l-OPLOPANONE

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Frank Norman Tuller

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GLOSSARY OF ABBREVIATIONS

DDHQ	2,3-Dicyano-5,6-dichlorobenzohydroquinone
DDQ	2,3-Dicyano-5,6-dichlorobenzoquinone
DMSO	Dimethylsulfoxide
glc	Gas Liquid Chromatography
Hz	Hertz
ir	Infrared
nm	Nanometer
nmr	Nuclear Magnetic Resonance
ppm	Parts per Million
SE-30	Silicone Gum Rubber (methyl)
THF	Tetrahydrofuran
TMS	Tetramethylsilane
uv	Ultraviolet

SUMMARY

The research described herein was of two parts. The first was to investigate further the photochemical rearrangement of 6/5-fused cross-conjugated cyclohexadienones with electron denoting substituents on the dienone chromophore. The second was to apply the results of these photochemical studies to the synthesis of natural products whose basic carbon skeletons are related to the carbon skeletons of the compounds which are obtained on irradiation of such cyclohexadienones.

The condensation of 1,4-dimethoxy-2-butanone (I) with 2-methyl cyclopentanone using known methods gave a 62 percent yield of 4-methoxy-7a-methyl-6,7-dihydro-5(7aH)-indanone (II) which was converted into 4-methoxy-7a-methyl-5(7aH)-indanone (III) in 53 percent yield. Various methods were used to convert II into III; each gave a different yield and percent conversion. Irradiation of III was carried out in glacial acetic acid using a 450-watt Hanovia high pressure lamp with a Pyrex probe to give an 85 percent yield of 3-methoxy-7 α -acetoxy-7 β -methyl-5,6,7,7a α -tetrahydro-2(4H)-indenone (IV).

A three-step procedure for preparing dihydropulegenone (V) in 55 percent yield from diethyl adipate was developed. Using known methods, V was condensed with I to give 2-(1-methoxy-2-butanone-4-yl)-2-methyl-5-isopropyl cyclopentanone (VI) in 25 percent yield. Base catalysed cyclization of VI gave 7,7a-dihydro-4-methoxy-7a-methyl-3-isopropyl-5(6H)-indanone (VII) in 63 percent yield. Spectral and chemical properties of VII indicated that the methyl and isopropyl

groups were cis oriented.

Compound VII was oxidized in 65 percent yield to 4-methoxy-7 α -methyl-3-isopropyl-5(7 α H)-indenone as two isomers, one with the methyl and the isopropyl groups cis (VIII) and one with the methyl and the isopropyl groups trans (IX). The two isomers were formed in the ratio of five parts VIII to one part IX, which was the equilibrium ratio. The isomers could be separated by chromatography on silica gel.

Irradiation of VIII in glacial acetic acid as described earlier gave a 91 percent yield of 3-methoxy-4 β -isopropyl-7 α -acetoxy-7 β -methyl-5,6,7,7 α -tetrahydro-2(4H)-indenone (X). When the five to one mixture of VIII and IX was irradiated, a five to one mixture of X and 3-methoxy-4 α -isopropyl-7 α -acetoxy-7 β -methyl-5,6,7,7 α -tetrahydro-2(4H)-indenone (XI) was obtained in 86 percent yield. Separation of X and XI was easily accomplished by fractional crystallization from an ether-hexane solvent. All attempts to convert XI into X were unsuccessful, leading only to loss of a molecule of acetic acid to form a linearly conjugated dienone.

Reduction of the ketone function of X followed by acylation of the alcohol led to a 94 percent yield of 2, 7 α -diacetoxy-3-methoxy-7 β -methyl-4 β -isopropyl-2,4,5,6,7,7 α -hexahydroindene (XII). Following a known procedure, XII was reduced with lithium in ethylamine to give a 67 percent yield of 7 α -hydroxy-4 β -isopropyl-3-methoxy-7 β -methyl-2,4,5,6,7,7 α -hexahydroindene (XIII). Kinetically controlled hydrolysis of XIII gave a 76 percent yield of 3 α -hydro-4 α -hydroxy-4 β -methyl-7 β -isopropyl-cis-perhydroindan-1-one (XIV). Thermodynamically controlled hydrolysis of XIII or equilibration of XIV gave 3 α -hydro-4 α -hydroxy-4 β -methyl-7 β -isopropyl-trans-perhydroindan-1-one (XV) in 73 percent or 96 percent yield

respectively.

Similarly, reduction of the ketone functions of XI followed by acylation of the alcohol gave an 86 percent yield of 2,7 α -diacetoxy-3-methoxy-7 β -methyl-4 α -isopropyl-2,4,5,6,7,7a α -hexahydroindene (XVI), which was then converted in 86 percent yield into 7 α -hydroxy-4 α -isopropyl-3-methoxy-7 β -methyl-2,4,5,6,7,7a α -hexahydroindene (XVII). Hydrolysis of XVII gave 3a α -hydro-4 α -hydroxy-4 β -methyl-7 α -isopropyl-cis-perhydroindan-1-one (XVIII).

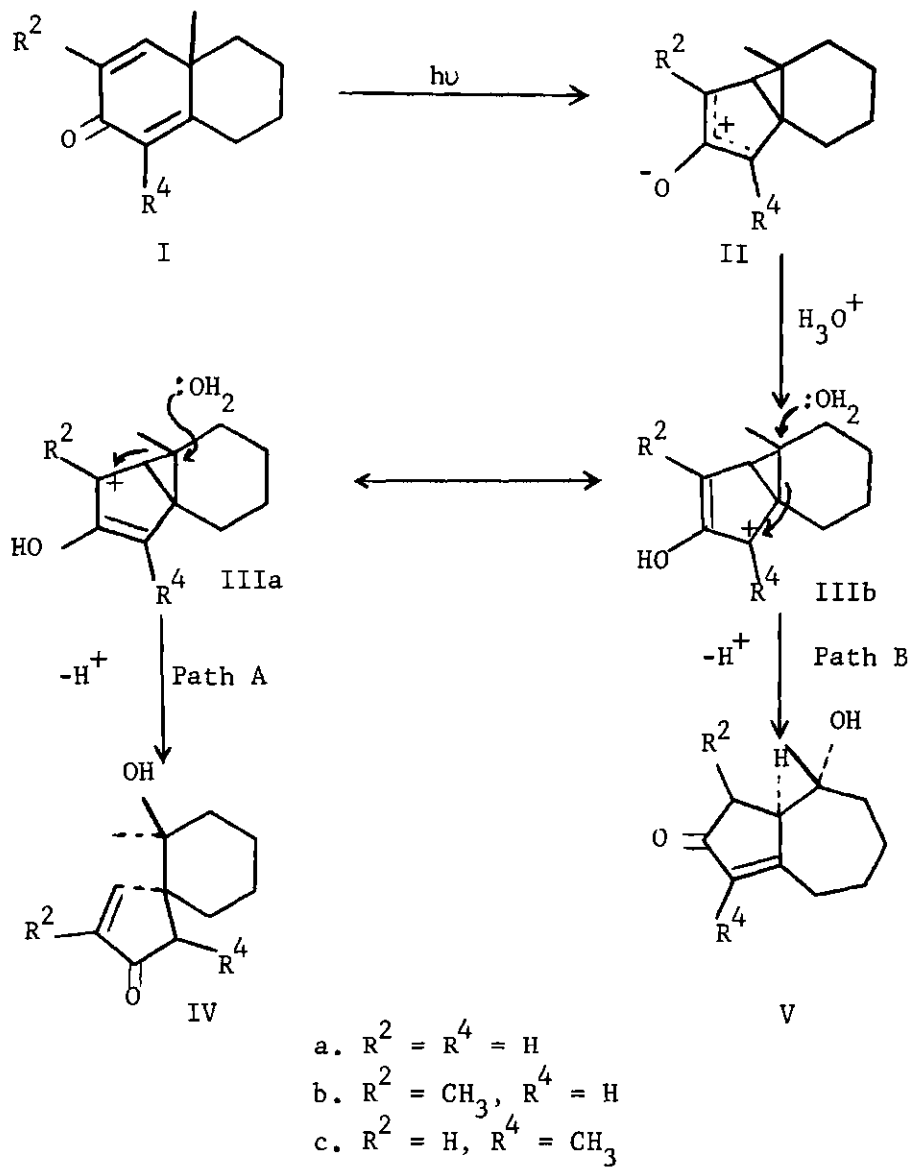
Conversion of XV into racemic oplopanone (XIX) proceeded by reaction with sodium acetylide to form an ethynyl carbinol and reaction of this ethynyl carbinol with mercuric acetate to form 1-acetoxy-1-acetyl-3a α -hydro-4 α -hydroxy-4 β -methyl-7 β -isopropyl-trans-perhydroindene (XX). Reductive removal of the acetoxy group from XX afforded XIX.

CHAPTER I

INTRODUCTION

Since Barton studied the photochemical rearrangement of α -santonin and elucidated some of the products (1), there has been much activity in the field of cross-conjugated cyclohexadienone photolysis. In most cases the compounds studied have been monocyclic, 6/6-fused bicyclic or steroidal dienones, and in all cases (2), irradiations in aqueous acidic media have been found to yield varying amounts of one or more hydroxy enone products. The structure of the hydroxy enones was found to depend significantly on the electronic nature of the substituents on the cyclohexadienone chromophore. Although the exact mechanistic details of the rearrangement are still unproven, it is widely accepted that the light-induced reaction produces a zwitterionic intermediate which in a protic solvent captures a proton to give a mesoionic species which then undergoes attack by solvent to yield hydroxy enone products. Several authors have suggested systems of notation for illustrating the pathways by which the zwitterionic intermediates might arise (3,4,5). As shown in Chart 1 (6), photolysis of I produces the resonance stabilized zwitterionic species II which in acidic media is protonated on the oxygen atom to produce the mesoionic species III. Here the electronic nature of a substituent at C-2 or C-4 becomes significant since it can influence the degree of importance of either IIIa or IIIb as contributing structures and thus influence whether subsequent reaction will favor path A or path B. Thus,

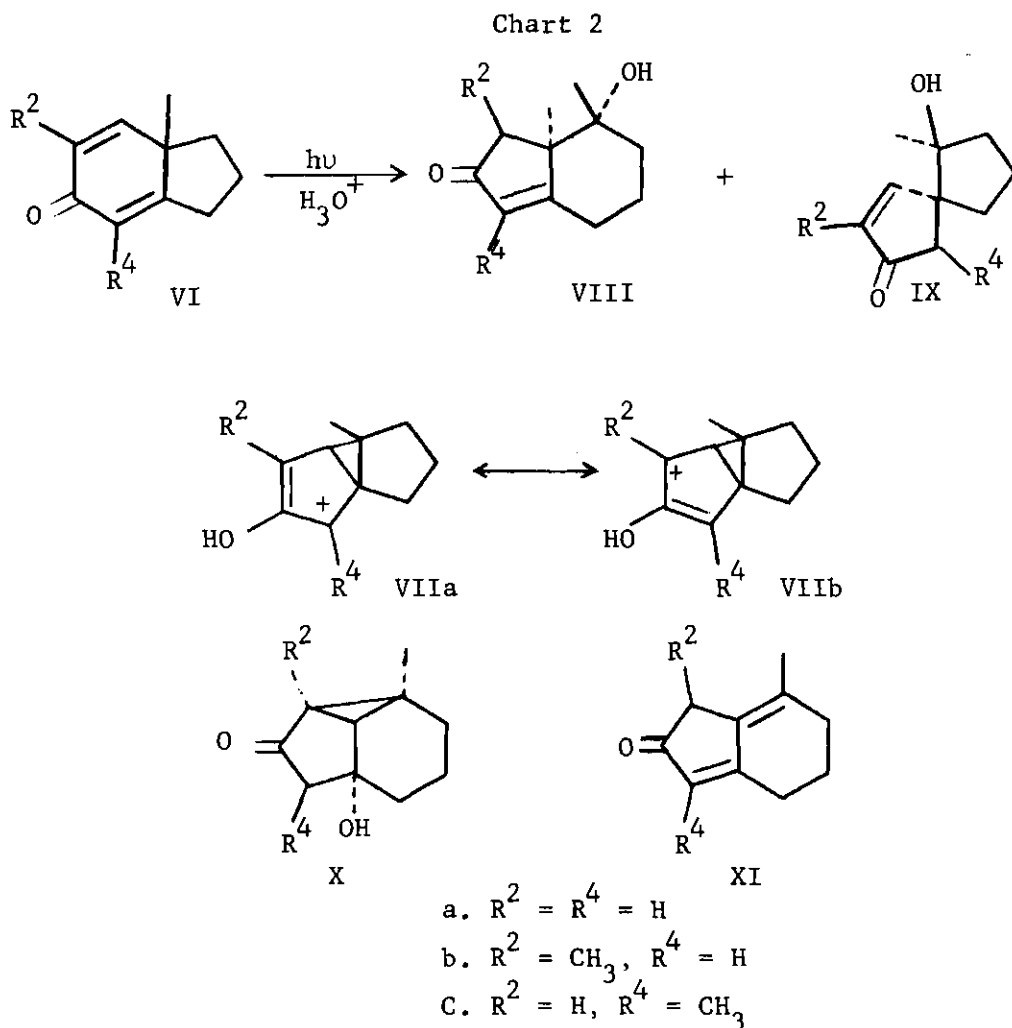
Chart 1



Mechanism of the Photochemical Rearrangement
of Cross-Conjugated Cyclohexadienones

if R^2 is electron releasing or R^4 is electron withdrawing, then IIIa is a more important contributor than IIIb, and the attack of water on III follows path A to yield the spiro-hydroxy ketone IV; whereas if the opposite is true with an electron withdrawing R^2 or electron releasing R^4 , the attack of water on III follows path B to produce the 5/7-fused hydroxy ketone V. As examples of this expected substituent influence, irradiation of Ia in 45 percent aqueous acetic acid gave a low yield of equal parts of IVa and Va in the product mixture since neither contributing structure of type III was favored and both pathways were followed. A similar irradiation of Ib (7) gave a 51 percent yield of exclusively IVb, while Ic (8) gave only Vc in an 80 percent yield. Effective appropriate substitution of the cyclohexadienone chromophore, therefore, not only helped control the course of the rearrangement but also noticeably increased the overall yield of hydroxy ketone photoproducts.

In recent years much work has been done to expand the studies of the photochemistry of cross-conjugated cyclohexadienones to include compounds with a 5 membered ring fused to the cyclohexadienone moiety. The first example of this was reported by Jeger and coworkers, who irradiated B-nor-1-dehydrotestosterone acetate in dioxane (9), but more extensive work in this area has been done by Caine and coworkers using simplified indanone derivatives (10,11,12,13). By extending the results of the 6/6-bicyclic compounds to the 6/5-bicyclic compounds as shown in Chart 2, one would expect the irradiation of compounds of type VI in aqueous acidic media to form the mesoionic species VII which would undergo attack by a solvent molecule to produce hydroxy ketone photoproducts of the type VIII or IX. However, the expected correspondence occurred only in the



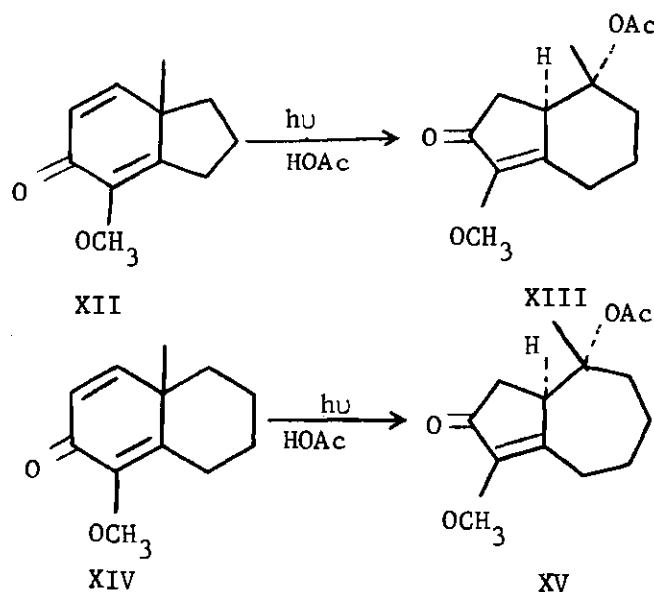
Photochemical Rearrangement of 6/5-Fused
Cross-Conjugated Cyclohexadienones

irradiation of VIc(10), which gave 60 percent of VIIIc in 45 percent aqueous acetic acid. The irradiation of VIa (12,13) in the same solvent produced a mixture of VIIa, Xa and XIa in the yields of 27 percent, 27 percent and 20 percent, respectively, while VIb (12,13) gave a mixture of VIIb, VIIIb and Xb in yields of 18 percent, 16 percent and 19 percent, respectively. These results indicated that while the photochemical rearrangements of 6/5-fused cyclohexadienones followed the example of their 6/6-fused analogues in the case of an electron donating substituent at C-4, new mechanisms and pathways were operative in the cases of

different or no substitution. Therefore, control of the rearrangement of 6/5-fused cyclohexadienones by the use of substituents on the chromophore appeared to be more complex and less rigid than it did for the 6/6-fused analogues.

An objective of the research described here was to study the photochemical rearrangement of the 6/5-fused cyclohexadienone XII with the electron donating C-4 methoxy substituent, as shown in Equation 1, in the hope that it would follow the example of its 6/6-fused analogue XIV, which on irradiation in glacial acetic acid gave XV exclusively (14). Glacial acetic acid was used instead of 45 percent aqueous acetic acid to avoid hydrolysis of the enol ether function. Thus irradiation of XII in glacial acetic acid was expected to yield the acetoxo ketone XIII.

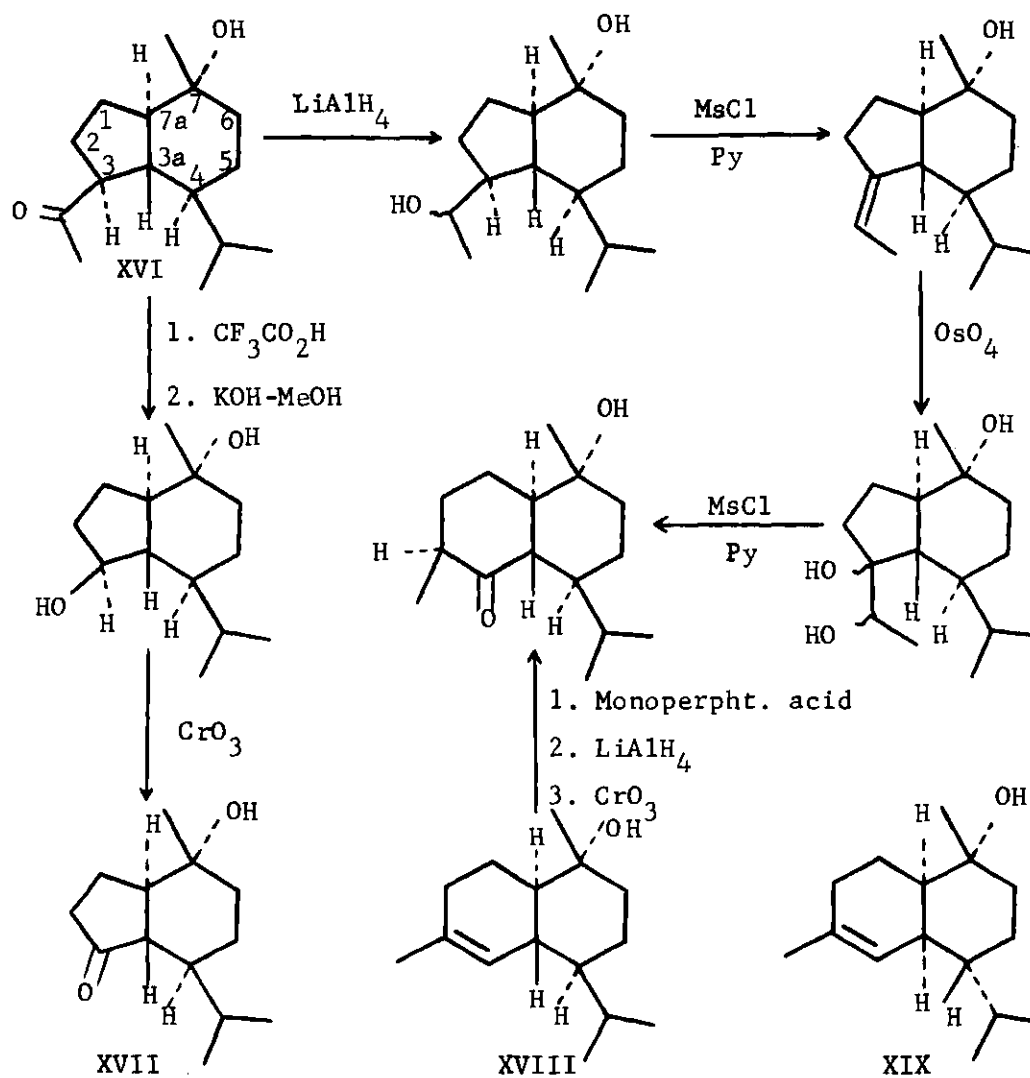
Eqn. 1



The photoproduct XIII was of much interest from a natural product synthesis point of view in that it had the same functions and stereochemistry at C-7 and C-7a as that reported for several naturally occurring compounds. The sesquiterpene oplopanone XVI, the structure of which was reported recently by H. Minato and coworkers (15a,b), has the same basic carbon skeleton as XIII plus the same configuration of methyl, hydroxyl and hydrogen functions at C-7 and C-7a. Other naturally occurring compounds that show similar stereochemistry are those of the α -cadinol (XVIII) family (16a,b) and the T-murrolol (XIX) family (17a,b) which require only a one carbon expansion of the A ring in type XIII photoproducts.

In the structure determination studies on oplopanone done by H. Minato (15a), the five-member ring was expanded to a six-member ring by the sequence shown in Chart 3 to give a hydroxy ketone identical to one which previously had been obtained from the sesquiterpene α -cadinol (XVIII) by Herout and coworkers (16a). This established the stereochemistry of oplopanone at C-4, C-7 and C-7a since the absolute configuration of α -cadinol had been completely elucidated (16a). The configuration at C-3a in oplopanone was established by degrading it to the hydroxy ketone XVII which was shown to have the same configuration at C-3a as that found in oplopanone. Ketone XVII was unchanged on treatment with alkali, indicating that it had the more stable trans ring fusion. An optical rotatory dispersion study of XVII showed a positive Cotton effect which indicated that the C-3a proton in XVII and, therefore,

Chart 3

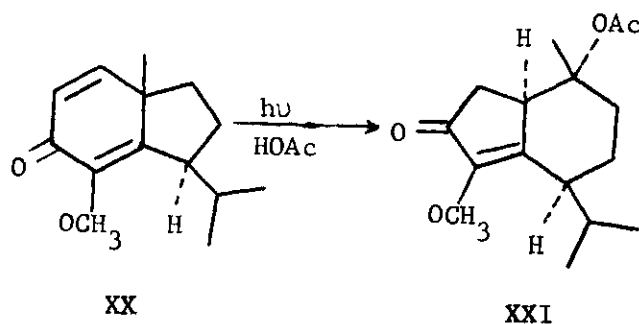


Structure Elucidation of Oplopanone

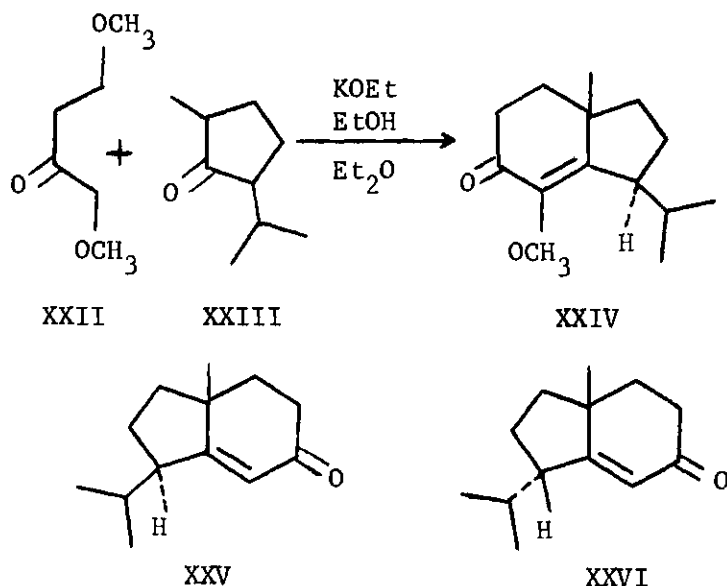
oplopanone was β -oriented. The configuration at C-3 in oplopanone was determined by its conversion into a diol by Baeyer-Villiger oxidation followed by saponification of the resulting acetate. It was assumed that the orientation of the C-3 hydroxy group in this diol would be the same as that of the acetyl side chain since the Baeyer-Villiger reaction proceeds with retention of configuration. The changes in optical rotation observed on converting this diol and its C-3 epimer, which was obtained as a minor product of metal hydride reductions of XVII, to corresponding benzoate esters indicated that the C-3 hydroxy group had the β -orientation. Thus, it was felt that the acetyl side chain of oplopanone also had a β -orientation. This was further supported by the fact that the ORD curve of oplopanone showed a negative Cotton effect.

The striking similarity between the degradation product XVII and the photoproduct XIII made the photolysis of a cyclohexadienone as described in equation 1 appear to be a very attractive route to the possible synthesis of oplopanone. Of the four centers of asymmetry in XVII (C-3a, C-4, C-7 and C-7a), the photoproduct XIII had two of the centers (C-7 and C-7a) with the correct stereochemistry. If the starting dienone XII had been substituted at C-5 with a β -oriented isopropyl group, this should have survived the photolysis unchanged to give the correct stereochemistry at C-4 in XVII. It had been reported by Minato (15a) that compound XVII was stable to base treatment in regard to epimerization at C-3a, so the stereochemistry at that site should follow from the equilibration of the ketone formed by the hydrolysis of the enol ether at C-3 in the photoproduct XIII. The removal of the unwanted ketone function at C-2 of XIII and the addition of the acetyl side chain at C-3 of XVII should be only minor problems in the synthesis of

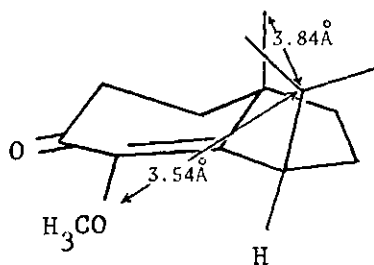
oplopanone. Therefore, the second goal of the research described herein was to synthesize the cyclohexadienone XX, study its photolysis in the hope of making XXI and then converting XXI into the sesquiterpene oplopanone.



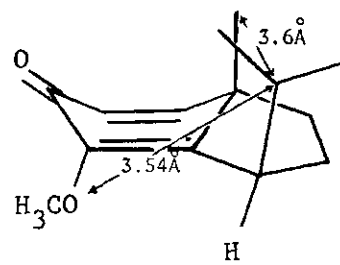
The precursor for XX should be the enone XXIV which should result from the condensation of 1,4-dimethoxy-2-butanone (XXII) with dihydropulegenone (XXIII) according to the procedure of Wenkert (18). A similar compound XXV has been reported by Levissaleles (19) as being a degradation product of the sesquiterpene (+)-carotol. When XXV was subjected to epimerizing conditions (perchloric acid with gentle warming) it was converted completely into the α -oriented isopropyl isomer XXVI which is energetically favored over XXV because of the 1,3-interaction between the methyl and the isopropyl groups in XXV. This 1,3-interaction is present in the cis form of dihydropulegenone XXIII and causes the cis/trans isomer ratio to be about 30 to 70 (20). The fusion of the 6-membered ring to XXIII caused the interaction to increase to the extent that none of XXV could be detected at equilibrium. In the case of compound XXIV, there is a 1,3-allylic interaction $[A^{1,3}(21)]$ between the isopropyl group and the methoxyl group which can more than offset the methyl-isopropyl



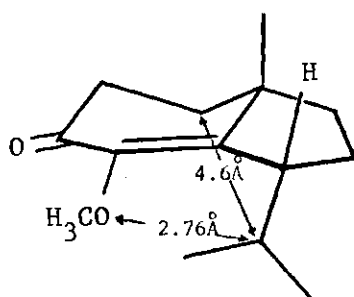
interaction. Using molecular models constructed from Dreiding Stereo-models the approximate distances between the central carbon atom of the isopropyl side chain and the carbon of the methyl group as well as the oxygen of the methoxyl group could be measured for the case of the β -isopropyl group, XXIV, and the α -isopropyl group, XXVII. The β -oriented isopropyl side chain should interact moderately with both the methyl group (C-C distance 3.84 Å) and the methoxyl group (C-O distance 3.54 Å) while the α -oriented isopropyl side chain has only a slight interaction with the C-1 carbon (C-C distance 4.6 Å) but a large interaction with the methoxyl group (C-O distance 2.76 Å). Using empirical correlations suggested by Hendrickson (22) or Bartell (23) that relate energy of interaction with distance of separation, a difference in energy between XXIV and XXVII can be qualitatively calculated at approximately 2 kcal/mole, which would indicate the predominance of XXIV by at least 96 percent.



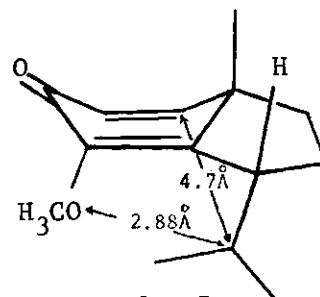
XXIV



XX



XXVII



XXVIII

The addition of the second double bond to make the cyclohexadiene chromophore needed for the photochemical rearrangement should not have any major effect on the molecule. In compound **XX** the interaction between the β -isopropyl group and the methyl group should increase slightly (C-C distance 3.60 Å) with methoxyl interaction remaining about the same (C-O distance still 3.54 Å), while in compound **XXVII** there is a decrease in the interaction of the α -oriented isopropyl group with both the C-1 carbon (C-C distance 4.70 Å) and the methoxyl group (C-O distance 2.88 Å) so that the difference in energy between **XX** and **XXVIII** should drop to approximately 1 kcal/mole by empirical calculations. This energy difference should indicate the predominance of **XX** by about 85 percent.

The mixture of **XX** and **XXVIII** should be easily separable by column chromatography due to the difference in geometry of the flatter molecule, **XX**, with the isopropyl and axial methyl groups on the same side of the

molecule and the rounder structure, XXVIII, with them on opposite sides. Once the β -oriented isopropyl isomer XX has been isolated, the stereochemistry of the isopropyl group should remain unchanged during the photolysis since in the photoproduct XXI the β -oriented isopropyl group has an equatorial configuration and thus is the most stable isomer.

There are many examples in the literature of the maintenance of the stereochemical integrity of C-5 substituents during photolysis (6). Therefore, the photochemical conversion of XX into XXI should easily provide a stereochemically controlled route to the total synthesis of racemic oplopanone.

CHAPTER II

INSTRUMENTATION AND EQUIPMENT

When required for a reaction, a nitrogen atmosphere was established using an apparatus similar to that described by Johnson (24). Removal of solvents in vacuo was done using a Buchi Rotavapor rotary evaporator. A Hanovia 450-watt high pressure mercury lamp in an all Pyrex apparatus similar to that described by Kropp and Erman (25) was the light source for the irradiations. A slow stream of dried, prepurified nitrogen was bubbled through the solution for 10 min prior to and during all irradiations for deoxygenation and agitation of the solution. Column chromatographies were carried out using Grace grade 923, 100-200 mesh silica gel in the ratio of 25 g silica gel per gram of mixture unless otherwise specified. Anhydrous sodium sulfate was used as drying agent in reaction workups. All inorganic chemicals used were commercially available reagent grade. All liquid organic reagents and solvents except ether were purified according to the procedures described by Fieser (26,27) and distilled prior to use. Ether, anhydrous and USP, was purchased commercially. All anhydrous solvents were stored over type 3A, 4A or 5A molecular sieves (28).

Infrared spectra were obtained using a Perkin-Elmer Model 137 or 457 recording spectrophotometer. For spectra run with a solvent, 0.1 mm sodium chloride cells were used. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60 or A-60D nuclear magnetic

resonance spectrometer or a Jeolco Model 4H-100 nuclear magnetic resonance spectrometer. Tetramethyl silane was used as an internal standard and the chemical shifts are reported in ppm downfield from it. The abbreviations s, d, d of d, t and m refer respectively to singlet, doublet, doublet of doublets, triplet and multiplet. Ultraviolet spectra were obtained using a Cary Model 14 recording spectrophotometer using one centimeter balanced cells; 95 percent ethanol was the solvent. Mass spectral data were obtained on a Varian Associates Model M-66 medium resolution mass spectrometer with a 70 electron volt source. Gas chromatographic analyses were done using a Perkin-Elmer Model 881 flame ionization gas chromatograph using a 6 ft by 1/8 in. stainless steel column packed with 10 percent K-20M Carbowax on 60/80 Chromasorb W HMDS with a temperature program of 100° to 200°C at 12 degrees per minute, or a 6 ft by 1/8 in. stainless steel column packed with 10 percent SE-30 on 80/100 Chromasorb W HMDS with a temperature program of 100° to 225°C at 12 degrees per minute. Preparative gas chromatography was performed on an Aerograph Model A-90P Manual Temperature Programmer Gas Chromatograph equipped with a thermal conductivity detector using a 3 ft by 1/4 in. stainless steel column packed with 15 percent 20M Carbowax on acid washed Firebrick at a temperature of 200° or a 10 ft by 1/4 in. stainless steel silanized column packed with 12 percent tris-(2-cyanoethoxy)-propane on 80/100 Diatoport S, which had been silanized with dichlorodimethylsilane, at a temperature of 170°C. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Boiling points are uncorrected. Carbon and hydrogen analyses were performed by either Galbraith Laboratories, Knoxville, Tennessee, or Atlantic Micro-lab, Inc., Atlanta, Georgia.

CHAPTER III

EXPERIMENTAL

7,7a-Dihydro-4-methoxy-7a-methyl-5(6H)-indanone (XXX)

Compound XXX was prepared by a method derived from that reported by Wenkert (18b). In a 500 ml three-neck flask equipped with a mechanical stirrer, dropping funnel, and Claisen head to allow having a thermometer inside the flask and a condenser with an inlet for nitrogen, which was established as the atmosphere, was placed 1.47 g (0.9376 mole) of potassium and 11 ml of absolute ethanol were added dropwise with stirring. After the reaction was complete and the flask had cooled to room temperature, 900 ml of anhydrous ether were added, and the mixture cooled with an ice bath to 10°C. To this was added 19.6 g (0.200 mole) of 2-methylcyclopentanone in 20 ml of anhydrous ether. A solution of 13.2 g (0.100 mole) of 1,4-dimethoxy-2-butanone (29) in 120 ml of anhydrous ether was added dropwise with rapid stirring over about 2 hr, while a temperature of 8-10°C was maintained with an ice bath. After the addition was complete, the reaction mixture was stirred for 3 hr longer while being warmed to room temperature. An ethereal solution of glacial acetic acid (10% by volume) was added dropwise until the red color of the reaction mixture changed to yellow. The ether layer was decanted from the solid, washed with 50 ml each of water and saturated brine, dried (Na_2SO_4), concentrated, and distilled giving 11.13 g (62%) of XXX as a colorless liquid: bp 85-88°C (0.51 mm). Redistillation of a small portion afforded an analytical sample: bp 73°C (0.04 mm);

uv max (95% EtOH) 254 nm (ϵ 8,260); ir (film) 1673 (α, β -unsaturated C=O), 1647 (conjugated C=C), 1210, 1110 and 1089 cm^{-1} ; nmr (CCl_4) δ 1.18 (s, 3H, 7a- CH_3), 1.62-2.02 (m, 6H, 1, 2 and 7- CH_2), 2.24-2.78 (m, 4H, 3 and 6- CH_2), and 3.54 ppm (s, 3H, 4- OCH_3); mass spectrum (70eV) m/e 180 (M^+) and 165 ($\text{M}^+ - \text{CH}_3$), EMD 180.11490 (calcd: 180.11494).

Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{O}_2$: C, 73.30; H, 8.95. Found: C, 73.34; H, 9.05.

4-Methoxy-7a-methyl-5(7aH)-indanone (XII)

Compound XII was prepared by a procedure similar to that employed by Burn, Kirk and Petrow (30). A 1000 ml round-bottom flask equipped with a magnetic stirrer and reflux condenser and having a nitrogen atmosphere, was charged with 400 ml p-dioxane (freshly distilled over sodium), 5.4 g (0.03 mole) of XXX and 7.02 g (0.031 mole) of 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ). The mixture was stirred until homogeneous and then stirred at reflux for 36 hr. After cooling to room temperature, the p-dioxane was removed in vacuo and the residue was dissolved in 100 ml of benzene and filtered to remove 2,3-dichloro-5,6-dicyano-p-hydroquinone (DDHQ). The filter cake was washed with 50 ml of benzene and the combined filtrates were concentrated. The residue was placed on a column of 50 g of neutral alumina and rapidly eluted with 500 ml of benzene. Evaporation of the benzene gave 3.86 g of a pale yellow oil which by glc analysis (Carbowax column) was shown to contain about equal amounts of XII and the starting material, XXX. Chromatography on 100 g of silica gel using hexane-ether as eluent afforded 1.85 g of the enone XXX (20% ether in hexane) and 1.80 g (51%) of the

dienone XII (40% ether in hexane). Distillation of a small portion of the latter afforded an analytical sample: bp 75°C (0.03 mm); uv max (95% EtOH) 242 nm (ϵ 5,430) and 276 nm (ϵ 1,371); ir (film) 1649 (α , β -unsaturated C=O), 1608 (conjugated C=C), 1452, 1208, 1152, 1081 and 840 cm^{-1} ; nmr (CCl_4) δ 1.22 (s, 3H, 7a- CH_3), 3.68 (s, 3H, 4- OCH_3) and 6.01 and 6.99 (AB quartet, $J_{\text{AB}} = 10\text{ Hz}$, 2H, 5,7-H); mass spectrum (70eV) m/e 178 (M^+) and 163 ($\text{M}^+ - \text{CH}_3$), EMD 178.09907 (Calcd: 178.09930).

Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_2$: C, 74.13; H, 7.92. Found: C, 74.12; H, 8.01.

In an alternate procedure, a solution of 3.51 g (0.0155 mole) of DDQ in 100 ml of anhydrous benzene was placed in a 250 ml round-bottom flask equipped with a magnetic stirrer, reflux condenser and nitrogen atmosphere. To this was added 2.79 g (0.0150 mole) of **XXX** and 3 ml of glacial acetic acid in 50 ml of anhydrous benzene. The mixture was stirred at reflux for 30 hr, cooled to room temperature, and filtered to remove DDHQ. The filter cake was washed with 50 ml of benzene and the combined filtrates were concentrated and placed on a column of 25 g of neutral alumina and rapidly eluted with 200 ml of benzene. Evaporation of the benzene left 2.06 g of a yellow oil which by glc analysis (Carbowax Column) was shown to be a 60-40 mixture of enone **XXX** and dienone XII.

In a procedure derived from that reported by Bernstein and Littell (31), a 1000 ml round-bottom flask was equipped with a magnetic stirrer, reflux condenser and nitrogen atmosphere. The flask was charged with 13.2 g (0.12 mole) of selenium dioxide (freshly prepared

and sublimed) dissolved in 500 ml of t-butyl alcohol (freshly distilled over sodium *t*-butoxide), and a solution of 5.40 g (0.03 mole) of **XXX** in 200 ml of t-butyl alcohol containing 2.5 ml of glacial acetic acid was added. The mixture was refluxed with rapid stirring for 40 hr, cooled to room temperature and filtered to remove metallic selenium. The solvent was removed in vacuo with gentle heating, leaving a black residue which was dissolved in 200 ml of ether. The ethereal solution was filtered to remove unreacted selenium dioxide, washed with saturated sodium bicarbonate solution until the washings remained alkaline and then once with saturated brine, dried (Na_2SO_4) and concentrated to yield a brown residue which was triturated with 3 x 50 ml of hot hexane. The combined hexane extracts were concentrated to afford 3.05 g of a yellow oil which on distillation gave 1.85 g (35%) of pure **XII**.

Irradiation of 4-Methoxy-7a-methyl-5(7aH)-indanone (**XII**)

A solution of 2.0 g of **XII** in 250 ml of glacial acetic acid (dried over 5A molecular sieves and distilled) was irradiated with a 450-watt high pressure mercury lamp for 4 hr using a Pyrex probe. The solution was washed into a 500 ml round-bottom flask with benzene, frozen quickly in a Dry Ice-acetone bath and the solvents removed by lyophilization to afford a yellow oil which on distillation gave 2.27 g (85%) of **XIII**: bp 102-105°C (0.05 mm); mp 54.5-55°C; uv max (95% EtOH) 252 nm (ϵ 11,300); ir (film) 1732 (ester C=O), 1710 (α,β -unsaturated C=O), 1650 (conjugated C=C), 1450, 1370, 1257, 1237 and 1098 cm^{-1} ; nmr (CCl_4) δ 1.28 (s, 3H, 7- CH_3), 1.97 (s, 3H, 7-OAc), 2.27 (d, $J = 4$ Hz, 2 H, 1- CH_2), 3.08 (t, $J = 4$ Hz, 1H, 7a-CH) and 3.90 ppm (s, 3H, 3-O CH_3);

mass spectrum (70 eV) m/e 178 ($M^+ - \text{HOAc}$).

Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_4$: C, 65.53; H, 7.61. Found: C, 65.26; H, 7.75.

2-Carbethoxy-2-isopropylcyclopentanone (XXXII)

A 3000 ml three-neck flask, equipped with a variable takeoff distilling head, a mechanical stirrer and an addition funnel, was flame dried and established with a dry nitrogen atmosphere. Potassium (30.1 g, 0.771 g-at) was introduced and 340 ml of absolute ethanol was added dropwise at a rate that allowed gentle reflux. After the reaction was complete, 136.4 g (0.675 mole) of diethyl adipate was added slowly with stirring, and the mixture was stirred at reflux for 7 hr. The ethanol (200 ml) was distilled and 1000 ml of dry toluene was added. Distillation was continued until the temperature of the vapor was 110°C . Often the addition of about 200-500 ml more of dry toluene was necessary during the distillation to sufficiently reduce the viscosity of the enolate sludge to allow efficient agitation. The mixture was allowed to cool slightly, and 131 g (0.77 mole) of 2-iodopropane was added. Stirring at reflux was continued for 12 hr, 30 g more of 2-iodopropane was added and stirring at reflux was continued for 12 hr. After the reaction mixture had been cooled to room temperature, 200 ml of water was added with stirring, the layers were separated and the aqueous layer was extracted with 100 ml of benzene. The combined organic layers were washed with saturated brine, concentrated, and distilled to give 110 g (82%) of XXXII: bp 90°C (1.5 mm) [lit. bp 112°C (11 mm) (32)] .

2-Methyl-5-isopropylcyclopentanone (XXIII)

Following the general procedure of Sisido (33), A 3000 ml three-neck flask, equipped with a variable takeoff distilling head, a mechanical stirrer and an addition funnel, was flame dried, established with a dry nitrogen atmosphere and charged with 750 ml of absolute ethanol. Sodium, 50 g (2.3 g-at), was added in small pieces at a sufficient rate to maintain slow reflux. After the sodium had reacted, 396 g (2.00 moles) of XXXII was added slowly and the mixture refluxed with rapid stirring for 7 hr. The ethanol (500 ml) was distilled, 1500 ml of dry toluene was added and distillation was continued until the temperature of the vapor was 110°C. The mixture was cooled to room temperature, 142 g (2.0 moles) of methyl iodide was added and stirring was continued for 8 hr at room temperature. Methyl iodide (40 g) was added and the mixture was stirred at reflux for 6 hr. After the reaction mixture cooled to room temperature, 200 ml of water was stirred into it, the layers were separated and the aqueous layer was extracted with 100 ml of benzene. The combined organic layers were washed with brine, concentrated, and returned to the 3000 ml three-neck flask along with 1200 ml of water and 600 ml of concentrated sulfuric acid. The mixture was refluxed with vigorous stirring for 24 hr, cooled to room temperature and the layers were separated. The aqueous layer was extracted with 3 x 100 ml of benzene, and the combined organic extracts were washed with 100 ml of water, 150 ml saturated sodium bicarbonate solution and 50 ml of water, dried (Na_2SO_4), concentrated and distilled to give 186 g (67%) of XXIII: bp 185°C (760 mm) [lit. bp 181-186°C (740 mm) (20)] .

2-(1-Methoxy-2-butanone-4-yl)-2-methyl-5-isopropylcyclopentanone (XXXIV)

In a procedure like that described for the preparation of XXX, a 5000 ml three-neck flask was equipped with a mechanical stirrer, dropping funnel and Claisen head fitted with a thermometer extending into the flask and a condenser with an inlet for nitrogen, which was established as the atmosphere. Potassium (13.2 g, 0.1128 g-at) was placed in the flask and 100 ml of absolute ethanol was added slowly. After the potassium had reacted and the flask had cooled, 900 ml of anhydrous ether was added, the mixture was cooled to 10°C and 252 g (1.8 moles) of XXIII in 120 ml of anhydrous ether was added. A solution of 132.0 g (1.0 mole) of 1,4-dimethoxy-2-butanone (29) in 1000 ml of anhydrous ether was added dropwise with rapid stirring over about 4 hr, while a temperature of 10-13°C was maintained with an ice bath. After the addition was complete, the reaction mixture was stirred for 3 hr longer while being allowed to warm to room temperature. An ethereal solution of glacial acetic acid (10% by volume) was added dropwise until the red color of the reaction mixture changed to yellow. Saturated sodium bicarbonate solution (200 ml) was added with stirring, the layers were separated and the aqueous layer was extracted with 100 ml of ether. The combined ethereal extracts were washed with water and dried (Na₂SO₄). The ether was removed in vacuo at room temperature and the unreacted XXIII (170 g) was removed by distillation at reduced pressure, bp 30-40°C (20 mm), maintaining the pot temperature at 75°C or below. The residue was further distilled to yield 35 g (25%) of XXXIV: bp 140-150°C (0.75 mm). A small portion was redistilled to afford an analytical sample: bp 113°C (0.25 mm); ir (film) 1729 (C=O), 1460, 1370, 1200 and 1108 cm⁻¹;

nmr (CCl_4) δ 0.90 and 0.98 (2s, 3H, 2- CH_3), 0.71 to 1.08 (m, 6H, 5-i-Pr), 3.35 (s, 3H, OCH_3) and 3.86 ppm (s, 2H, $\text{CO}-\text{CH}_2-\text{O}$); mass spectrum (70 eV) m/e 240 (M^+) and 195 ($\text{M}^+-\text{CH}_2\text{OCH}_3$), EMD 240.17243 (calcd: 240.17241).

Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{O}_3$: C, 69.96; H, 10.07. Found: C, 70.09, H, 10.16.

7,7a-Dihydro-4-methoxy-7a-methyl-3-isopropyl-5(6H)-indanone (XXIV)

In a 500 ml round-bottom flask fitted with a reflux condenser and a magnetic stirrer and maintained under a nitrogen atmosphere, 20.0 g of potassium hydroxide was dissolved in 200 ml of absolute ethanol and 20.0 g (0.083 mole) of XXXIV was added. After being stirred at reflux for 1 hr, the reaction mixture was cooled, and glacial acetic acid was added dropwise with stirring until the red color of the solution had turned yellow (usually about 20 ml). The ethanol was removed in vacuo and the residue was mixed with ether and water. The layers were separated, the aqueous layer was extracted with ether and the combined ethereal solutions were washed with 50 ml each of saturated sodium bicarbonate and water, dried (Na_2SO_4), concentrated and distilled to yield 11.6 g (63%) of XXIV: bp $100-105^\circ\text{C}$ (0.45 mm). Redistillation of a small portion afforded an analytical sample: bp $89-90^\circ\text{C}$ (0.04 mm); uv max (95% EtOH) 259 nm (ϵ 7,969); ir (film) 1675 (α,β -unsaturated $\text{C}=\text{O}$), 1631 ($\text{C}=\text{C}$), 1461, 1295, 1209, 1112 and 1085 cm^{-1} ; nmr (CCl_4) 0.83 and 0.95 (d of d, $J = 7\text{ Hz}$, 6H, 3- CH_3CHCH_3), 1.19 (s, 3H, 7a- CH_3) and 3.61 ppm (s, 3H, 4- OCH_3); mass spectrum (70eV) m/e 222 (M^+), 207 (M^+-CH_3) and 179 ($\text{M}^+-\text{CH}_3\text{CHCH}_3$), EMD 222.16196 (Calcd: 222.16186).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.44; H, 9.71.

In an alternate experiment the procedure described above was repeated except that instead of refluxing the reaction mixture for 1 hr, it was stirred at room temperature for 7 d. Distillation of the crude reaction product gave 12.5 g (68%) of XXIV: bp 95-110°C (0.3 mm). Analysis of the distillate by glc showed it to contain one component.

Attempted Conversion of XXIV into its C-3 Epimer

In a 100 ml three-neck flask fitted with a reflux condenser, addition funnel, and magnetic stirrer and maintained under a nitrogen atmosphere was placed 1.17 g (0.03 g-at) of potassium and 30 ml of t-butyl alcohol (freshly distilled over sodium t-butoxide) was added dropwise with stirring. After the addition was complete and the potassium had reacted completely, a solution of Compound XXIV (2.22 g, 0.01 mole) in 10 ml of t-butyl alcohol was added and the mixture was refluxed and stirred overnight. After the reaction mixture had cooled to room temperature, 1.80 g (0.03 mole) of glacial acetic acid in 10 ml of t-butyl alcohol was added dropwise rapidly with stirring. The solvent was removed by lyophilization, the residue was dissolved in ether and the ethereal solution was washed with water, dried (Na_2SO_4) and concentrated to yield a yellow oil (2.22 g) which could not be differentiated from starting XXIV by glc (Carbowax column) or nmr analysis.

4-Methoxy-7a-methyl-3-isopropyl-5(7aH)-indanone (XX)

A 5000 ml three-neck flask fitted with a mechanical stirrer and variable takeoff distilling head and containing a nitrogen atmosphere was flame dried and charged with 22.2 g (0.200 mole) of freshly sublimed selenium dioxide, 3000 ml of t-butyl alcohol (freshly distilled over sodium t-butoxide) and 10 ml of glacial acetic acid. The mixture was stirred with warming until all of the selenium dioxide had dissolved and a solution of 11.1 g (0.05 mole) of XXIV in 500 ml of t-butyl alcohol was added. After the reaction mixture had been stirred at reflux for four days, 3000 ml of t-butyl alcohol were removed by distillation. The remaining suspension was cooled and filtered through a fritted glass funnel to remove metallic selenium. The filtrate was concentrated in vacuo and the residue was dissolved in 500 ml of ether and filtered again to remove unreacted selenium dioxide. The ethereal filtrate was stirred well with 200 ml of saturated sodium carbonate solution and solid sodium carbonate was added slowly until evolution of carbon dioxide ceased. The ether-water mixture was filtered with suction and the filter cake was washed well with ether. The layers were separated, and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with water, dried (Na_2SO_4) and concentrated. The residue was triturated with 3 x 75 ml of hot hexane, and the hexane extracts were concentrated and distilled to give 8 g of a yellow oil, bp 90-100°C (0.3mm), which by glc analysis (Carbowax column) was shown to be a 3:1 mixture of dienone product and enone XXIV. Chromatography on 200 g neutral alumina using hexane-ether as the elutant afforded 1.95 g of XXIV (10% ether in hexane) and 5.92 g (65%) of dienone product (25% ether in hexane). Analysis by

glc (tris-cyanoethoxy-propane column) and nmr showed that the dienone product was actually a 5:1 mixture of isomers having the C-3 isopropyl group in the β and α configurations, respectively. Careful chromatography on silica gel permitted the isolation of the pure components of this mixture. The physical properties of the 3β -isopropyl compound **XX** were: bp $94-97^{\circ}\text{C}$ (0.07 mm); uv max (95% EtOH) 243 nm (ϵ 4,145) and 283 nm (ϵ 1,113); ir (film) 1659 (α, β -unsaturated C=O), 1608 (C=C), 1462, 1370, 1330, 1213, 1148, 1077 and 840 cm^{-1} ; nmr (CCl_4) δ 0.92 and 0.97 (d of d, $J = 11\text{ Hz}$, 6H, $3\beta\text{-CH}_3\text{CHCH}_3$), 1.21 (s, 3H, 7a- CH_3), 3.79 (s, 3H, 4-O CH_3) and 5.99 and 6.88 ppm (AB quartet, $J_{\text{AB}} = 10\text{ Hz}$, 2H, 6,7-H); mass spectrum (70eV) m/e 220 (M^+), 205 ($\text{M}^+ - \text{CH}_3$) and 177 ($\text{M}^+ - \text{CH}_3\text{CHCH}_3$), EMD 220.14607 (Calcd: 220.14622).

Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2$: C, 76.33; H, 9.15. Found: C, 76.06; H, 9.26.

The physical properties of the 3α -isopropyl isomer **XXVIII** were: bp $94-97^{\circ}\text{C}$ (0.07 mm); uv max (95% EtOH) 243 nm (ϵ 6,700) and 283 nm (ϵ 3,600); ir (film) 1661 (α, β -unsaturated C=O), 1609 (C=C), 1460, 1370, 1211, 1150, 1073 and 840 cm^{-1} ; nmr (CCl_4) δ 0.68 and 0.97 (d of d, $J = 11\text{ Hz}$, 6H, $3\alpha\text{-CH}_3\text{CHCH}_3$), 1.22 (s, 3H, 7a- CH_3), 3.69 (s, 3H, 4-O CH_3) and 5.99 and 6.94 ppm (AB quartet, $J_{\text{AB}} = 10\text{ Hz}$, 2H, 6,7H); mass spectrum (70eV) m/e 220 (M^+), 205 ($\text{M}^+ - \text{CH}_3$) and 177 ($\text{M}^+ - \text{CH}_3\text{CHCH}_3$), EMD 220.14632 (calcd: 220.14622).

Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2$: C, 76.33; H, 9.15. Found: C, 76.51; H, 9.34.

In an attempted oxidation of **XXIV** with DDQ, a 1000 ml round-bottom flask fitted with a reflux condenser and a magnetic stirrer and containing

a nitrogen atmosphere was flame dried and charged with 10.0 g (0.044 mole) of DDQ and 400 ml of *p*-dioxane (freshly distilled over sodium). The mixture was stirred until homogeneous, and 8.88 g (0.04 mole) of XXIV in 10 ml of *p*-dioxane was added. After being stirred at reflux for 36 hr the mixture was cooled, filtered and concentrated in vacuo. The residue was placed on a column of 75 g of neutral alumina and rapidly eluted with 750 ml of benzene. The benzene solution was concentrated and distilled to give 5.74 g of a yellow oil; bp 95°C (0.28 mm). Analysis by glc (Carbowax column) showed the oil to be a mixture of about 50% of starting XXIV, 5% of cross-conjugated dienone XX and 45% of a compound which, on the basis of its nmr spectral properties, appeared to be the linear dienone XXXIX.

In an attempted oxidation of XXIV with lead tetraacetate, a 100 ml round-bottom flask fitted with a reflux condenser and a magnetic stirrer and maintained under a nitrogen atmosphere was charged with 50 ml of glacial acetic acid, 5 ml of acetic anhydride, 5 g of sodium acetate, 4.44 g (0.0200 mole) of XXIV and 14.6 g (0.0333 mole) of lead tetraacetate. After being stirred at reflux for 48 hr, the mixture was concentrated by lyophilization and the residue was taken up in 50 ml of ether. The ethereal solution was carefully washed with saturated sodium bicarbonate solution until the washings remained alkaline, then with water, dried (Na_2SO_4) and concentrated to give a brown oil which by glc (Carbowax column) and nmr analysis appeared to be 70% unreacted XXIV and 30% C-6 acetoxy compound XLII. No evidence for any dienone formation was seen.

Attempted Conversion of XX into its C-3 Epimer

In a 25 ml three-neck flask fitted with a reflux condenser, mechanical stirrer and an addition funnel and maintained under a nitrogen atmosphere was placed 0.012 g (0.00033 g-at) of potassium and 10 ml of dry *t*-butyl alcohol. After the potassium had reacted, 0.67 g (0.0033 mole) of the 5 to 1 mixture of XX and XXVIII in 10 ml of dry *t*-butyl alcohol was added and the mixture was stirred at reflux overnight. After it had cooled and 0.018 g (0.0003 mole) of glacial acetic acid in 10 ml *t*-butyl alcohol had been added, the mixture was concentrated by lyophilization and the residue was dissolved in ether. The ethereal solution was washed with water, dried (Na_2SO_4) and concentrated to give a brown oil, which by glc (Carbowax column) and nmr analysis could not be distinguished from the starting material.

Following the procedure of Tanabe and Crowe (34) a 100 ml three-neck flask with a mechanical stirrer and a reflux condenser was charged with 1.12 g (0.0100 mole) of potassium *t*-butoxide, 10 ml of dry dimethyl sulfoxide and 0.220 g (0.00100 mole) of the 5 to 1 mixture of XX and XXVIII. The mixture was stirred at room temperature for 1.5 hr, and 50 ml of 10% aqueous acetic acid was added rapidly with vigorous stirring. The mixture was extracted with 4 x 50 ml of ether, and the ethereal extracts were washed with saturated sodium bicarbonate solution and water, dried (Na_2SO_4) and concentrated to give a yellow oil which could not be identified by glc or nmr analysis. No absorption for methoxy protons appeared in the nmr spectrum and there was no evidence that the desired epimerization had occurred.

Irradiation of 4-Methoxy-7 α -methyl-3-isopropyl-5(7 α H)-indanone (XX)

A 5:1 mixture of 3 β -isopropyl XX and 3 α -isopropyl XXVIII (2.0 g) was dissolved in 250 ml of glacial acetic acid (dried over 5A molecular sieves and distilled) and irradiated with a 450-watt high pressure mercury lamp for 4 hr using a Pyrex probe. The solution was washed into a 500 ml round-bottom flask with benzene, frozen quickly in a Dry Ice-acetone bath, and the solvent removed by lyophilization to afford 2.20 g (86%) of a yellow solid. Fractional crystallization from hexane afforded 1.80 g of 3-methoxy-4 β -isopropyl-7-acetoxy-7-methyl-5,6,7,7 α -tetrahydro-2(4H)-indenone (XXI) and 0.36 g of 3-methoxy-4 α -isopropyl-7-acetoxy-7-methyl-5,6,7,7 α -tetrahydro-2(4H)-indenone (XLIV). The physical properties of XXI were: bp 123°C (0.05 mm); mp 73-74.5°C; uv max (95% EtOH) 252 nm (ϵ 9,800); ir (CCl₄) 1738 (OAc), 1714 (α , β -unsaturated C=O), 1630 (C=C), 1444, 1383, 1370, 1250, 1237 and 1102 cm⁻¹; nmr (CCl₄) δ 0.88 and 0.97 (d of d, J = 6 Hz, 6H, 4 β CH₃CHCH₃), 1.22 (s, 3H, 7-CH₃), 1.91 (s, 3H, 7-OAc), 2.18 (d, J = 4.5 Hz, 2H, 1-CH₂), 3.01 (t, J = 4.5 Hz, 1H, 7 α -CH) and 3.84 ppm (s, 3H, 3-OCH₃); mass spectrum (70eV) m/e 220 (M⁺-HOAc).

Anal. Calcd for C₁₆H₂₄O₄: C, 68.54; H, 8.63. Found: C, 68.33; H, 8.79.

The physical properties of XLIV were: mp 98-99°C; uv max (95% EtOH) 254 nm (ϵ 10,900); ir (CCl₄) 1733 (OAc), 1709 (α , β -unsaturated C=O), 1643 (C=C), 1448, 1371, 1249, 1232 and 1098 cm⁻¹; nmr (CCl₄) δ 0.84 and 1.02 (d of d, J = 6 Hz, 6H, 4 α -CH₃CHCH₃), 1.28 (s, 3H, 7-CH₃), 1.97 (s, 3H, 7-OAc), 2.30 (d, J = 4 Hz, 2H, 1-CH₂), 3.21 (t, J = 4 Hz, 1H, 7 α -CH) and 3.90 ppm (s, 3H, 3-OCH₃); mass spectrum (70eV) m/e 220

($M^+ - \text{HOAc}$).

Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_4$: C, 68.54; H, 8.63. Found: C, 68.76; H, 8.47.

A solution of 0.90 g of pure C-3 β isopropyl dienone **XX** in 250 ml of glacial acetic acid (freshly dried) was irradiated with a 450-watt high pressure mercury lamp for 4 hr using a Pyrex probe, washed into a 500 ml round-bottom flask with benzene and concentrated by lyophilization of the solvents to give 1.04 g (91%) of solid **XXI**. Distillation in a Hickman microstill afforded pure **XXI**: bp 120-125°C (0.05 mm). The isomeric photoproduct **XLIV** was not observed in either the crude or the distilled product in this run.

Attempted Equilibration of **XXI** and **XLIV**

A solution of a 3:2 mixture of **XXI** and **XLIV** in carbon tetrachloride in an nmr tube was treated with trifluoroacetic acid, and the nmr spectrum of the mixture was taken at various time intervals. After 2 hr at room temperature, no change had occurred. After one week at room temperature, the spectrum indicated that acetic acid had been eliminated and the linear dienone **XLV** had been formed. In an attempted base catalysed epimerization, a 3:2 mixture of **XXI** and **XLIV** was dissolved in DMSO-d_6 and treated with 0.33 equivalents of sodium deuterioxide in deuterium oxide. After one half hour nmr analysis of the reaction mixture showed that the complete conversion of the mixture into **XLV** had taken place. Treatment of a 3:2 mixture of **XXI** and **XLIV** with pyrrolidene and *p*-toluenesulfonic acid produced no detectable change in the nmr spectrum of the mixture.

2,7-Diacetoxy-3-methoxy-7-methyl-4 β -isopropyl-

2,4,5,6,7,7a-hexahydroindene (XLVI)

A 10 ml round-bottom flask fitted with a magnetic stirrer and maintained under a nitrogen atmosphere was charged with 0.526 g (0.0188 mole) of XXI, 0.0720 g (0.00188 mole) of sodium borohydride and 8 ml of absolute ethanol; the reaction mixture was stirred at room temperature for 2 d. Acetone (1 ml) was added and, after the mixture was stirred for 2 hr, the volatile material was removed in vacuo with warming. The residue was dissolved in a mixture of 10 ml ether and 10 ml water; the layers were separated, and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with water, dried (Na_2SO_4) and concentrated to give 0.6352 g of a pale yellow oil, which was shown to be the expected alcohol **XLIX**, by nmr and ir analysis. The crude reaction product was placed in a 10 ml round-bottom flask fitted with a magnetic stirrer and maintained under a nitrogen atmosphere along with 1.5 g of acetic anhydride and 8 ml of dry pyridine and the mixture was stirred for 20 hr at room temperature. After cooling the reaction mixture to 0°C with an ice bath, 2 g of ice was added and the mixture stirred for 2 hr while being allowed to warm to room temperature. The mixture was poured into 50 ml of ether and washed with water. The aqueous layer was extracted with 20 ml of ether and the combined ether extracts were washed with 5 ml portions of 10% aqueous sulfuric acid until the washing remained acidic. The ether layer was washed with saturated sodium bicarbonate, dried (Na_2SO_4) and concentrated to give 0.5719 g (94%) of XLVI as a viscous oil. Crystallization from hexane at -78°C afforded a material which melted upon warming to room temperature:

ir (film) 1720 (ester C=O), 1668 (C=C), 1448, 1369, 1243, 1090 and 1018 cm^{-1} ; nmr (CCl_4) δ 0.89 and 0.93 (d of d, $J = 6$ Hz, 6H, $4\beta\text{CH}_3\text{CHCH}_3$), 1.27 and 1.33 (s, 3H, 7CH_3 of two isomers), 1.89 (s, 3H, 7-OAc), 2.01 (s, 3H, 2-OAc), 3.51 (s, 3H, 3-OCH₃) and 5.63-5.92 ppm (m, 1H, 2-H); mass spectrum (70eV) m/e 264 ($\text{M}^+ - \text{HOAc}$).

Anal. Calcd for $\text{C}_{18}\text{H}_{28}\text{O}_5$: C, 68.06; H, 9.28. Found: C, 68.32; H, 9.37.

2,7-Diacetoxy-3-methoxy-7-methyl-4 α -isopropyl-

2,4,5,6,7,7a-hexahydroindene (LIII)

Following exactly the same procedure described above, a 10 ml round-bottom flask was charged with 0.526 g (0.00188 mole) of XLIV, 0.0720 g (0.00188 mole) of sodium borohydride and 8 ml of absolute ethanol; the reaction mixture was stirred for 2 d. The work-up gave 0.5469 g of the expected alcohol as a pale yellow oil which was acetylated using 1.5 g acetic anhydride and 8 ml of dry pyridine as described above to yield 0.5214 g (86%) of LIII. Crystallization from ether-hexane at -20°C afforded an analytical sample: ir (film) 1728 (ester C=O), 1688 (C=C), 1458, 1368, 1238, 1072 and 1020 cm^{-1} ; nmr (CCl_4) δ 0.78 and 0.94 (d of d, $J = 6$ Hz, 6H, $4\alpha\text{CH}_3\text{CHCH}_3$), 1.35 (s, 3H, 7-CH₃), 1.88 (s, 3H, 7-OAc), 1.98 (s, 3H, 2-OAc), 2.79 and 2.92 (d of d, $J = 3$ Hz, 1H, 7a-H), 3.53 (s, 3H, 3-OCH₃) and 5.70 and 5.83 ppm (d of d, $J = 2$ Hz, 1H, 2H); mass spectrum (70eV) m/e 264 ($\text{M}^+ - \text{HOAc}$).

Anal. Calcd for $\text{C}_{18}\text{H}_{28}\text{O}_5$: C, 68.06; H, 9.28. Found: C, 67.85; H, 9.14.

Attempted Synthesis of 2-Acetoxy-3-methoxy-4 β -isopropyl-7 α -hydroxy-7 β -methyl-2,4,5,6,7,7a-hexahydroindene (L)

A 50 ml three-neck flask, equipped with a stirrer and an addition funnel, and maintained under a nitrogen atmosphere was charged with 0.140 g (0.00050 mole) of XXI dissolved in 10 ml of anhydrous ether, and the mixture was cooled to 0°C with an ice bath. A saturated solution of lithium aluminum hydride in anhydrous ether [1.15 ml of solution containing 0.0285 g LiAlH₄ (0.000750 mole)] diluted with 10 ml of anhydrous ether was added dropwise over one hour at 0°C with stirring, and stirring was continued for 4 hr while the mixture was allowed to warm to room temperature. A saturated sodium sulfate solution was added slowly with stirring until the ether solution became clear and a white precipitate had formed. The ethereal supernate was decanted and the precipitate washed several times with ether. The combined ether washings were dried (Na₂SO₄) and concentrated to yield 0.1722 g of a yellow oil which had nmr and ir spectra consistent with the expected diol structure LI. A solution of 0.150 g of this yellow oil, 3 ml of dry pyridine and 0.60 g of acetic anhydride was stirred at room temperature under a nitrogen atmosphere for 20 hr. After cooling the reaction to 0°C with an ice bath, 0.5 g of ice was added and the mixture was stirred for 2 hr while being allowed to warm to room temperature. The mixture was poured into 50 ml of ether and washed with water. The aqueous layer was extracted with 20 ml of ether and the combined ethereal extracts were washed with 5 ml portions of 10% aqueous sulfuric acid until the washings remained acidic, then with saturated sodium bicarbonate, dried (Na₂SO₄) and concentrated to give 0.090 g of a brown oil which was subjected to

chromatography on silica gel. Examination of the elutant fractions by spectroscopic methods showed that none of these contained material having properties consistent with those of the expected hydroxy-acetate L.

3 α -Hydro-4 α -hydroxy-4 β -methyl-7 β -isopropyl-
trans-perhydroindan-1-one (XVII)

Into a 50 ml three-neck flask equipped with a glass magnetic stirrer and a Dewar condenser and maintained under a nitrogen atmosphere was distilled 30 ml of ethylamine (distilled over lithium), and it was cooled to -78°C in a Dry Ice-isopropyl alcohol bath. A solution of 0.696 g (0.00215 mole) of XLVI and 0.159 g (0.00215 mole) of dry t-butyl alcohol in 15 ml of anhydrous ether was added, followed by about 0.05 g of freshly cut pieces of lithium wire. The reaction mixture was stirred vigorously at -78°C until the blue color persisted throughout the solution and then for one hour longer. The reaction mixture was rapidly filtered through glass wool into a flask containing about 0.1 g solid ammonium chloride and swirled to destroy the excess lithium. The supernate was decanted and concentrated in vacuo, and the residue was dissolved in a mixture of ether and water. The layers were separated, and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with brine, dried (Na_2SO_4) and concentrated to give 0.4146 g of a yellow oil which upon Hickman microdistillation yielded 0.3208 g (67%) of the enol ether XLVII [bath temperature $100-105^{\circ}\text{C}$ (0.05 mm)] : nmr (CCl_4) δ 0.82 and 0.92 (d of d, $J = 6$ Hz, 6H, $7^{\beta}\text{CH}_3\text{CHCH}_3$), 0.99 (s, 3H, 4- CH_3) and 3.48 ppm (s, 3H, OCH_3). A solution of 0.309 g (0.00140 mole) of XLVII, 6 ml of methanol and 2 ml of water containing

0.027 g (0.00030 mole) of oxalic acid was stirred at room temperature for 2 hr and 0.5 ml of saturated sodium bicarbonate solution was added. The solvents were removed in vacuo, and the residue was dissolved in ether and water. The layers were separated, and the aqueous layer was extracted with ether. The combined ethereal layers were washed with brine, dried (Na_2SO_4) and concentrated to give a yellow oil which yielded 0.2108 g (73%) of XVII upon Hickman microdistillation [bath temperature 102-108°C (0.07 mm)]: mp 79-80°C, ir (CCl_4) 3520 (OH), 1730 (C=O), 1466, 1381, 1158, 1120 and 1056 cm^{-1} ; nmr (CCl_4) δ 0.77 and 0.92 (d of d, $J = 6$ Hz, 6H, $7\beta\text{-CH}_3\text{CHCH}_3$) and 1.14 ppm (s, 3H, CH_3); mass spectrum (70eV) m/e 210 (M^+), EMD 210.16201 (calcd: 210.16186).

Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_2$: C, 74.29; H, 10.47. Found: C, 74.00; H, 10.36.

3 α -Hydro-4 α -hydroxy-4 β -methyl-7 β -isopropyl-

cis-perhydroindan-1-one (XLVIII)

A 5 ml round-bottom flask fitted with a magnetic stirrer and containing a nitrogen atmosphere was charged with a solution of 0.045 g (0.00020 mole) of XLVII, 2 ml of methanol and 0.5 ml of water with 0.002 g of oxalic acid. The mixture was stirred for 0.5 hr at room temperature and 5 drops of saturated sodium bicarbonate solution were added. The solvents were removed in vacuo, and the residue was dissolved in ether and water (10 ml each). The layers were separated, and the aqueous layer was extracted with ether. The combined ethereal layers were washed with brine, dried (Na_2SO_4) and concentrated to give a yellow oil that yielded 0.0320 g (76%) of XLVIII upon Hickman microdistillation [bath temperature

100-105°C (0.05 mm)]: ir (film) 3490 (OH), 1734 (C=O), 1470, 1390, 1160 and 1120 cm^{-1} ; nmr (CCl_4) δ 0.88 and 0.90 (d of d, $J = 7$ Hz, 6H, $7\beta\text{-CH}_3\text{CHCH}_3$) and 0.96 ppm (s, 3H, CH_3); mass spectrum (70eV) m/e 210 (M^+), EMD 210.16192 (calcd: 210.16186).

Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_2$: C, 74.29; H, 10.47. Found: C, 74.36; H, 10.60.

3 α -Hydro-4 α -hydroxy-4 β -methyl-7 α -isopropyl-
cis-perhydroindan-1-one (LII)

In a procedure similar to that described for the preparation of XVII, 30 ml of ethylamine (freshly distilled over lithium wire while the blue color persisted) was collected in a 50 ml three-neck flask equipped with a glass magnetic stirrer and Dewar condenser and maintained under a nitrogen atmosphere, and was cooled to -78°C with a Dry Ice-isopropyl alcohol bath. A solution of 0.389 g (0.00120 mole) of LIII and 0.0889 g (0.00120 mole) of dry t-butyl alcohol in 15 ml of anhydrous ether was added, followed by about 0.05 g of freshly cut lithium wire. As before, the reaction mixture was stirred vigorously at -78°C until the blue color persisted throughout the solution and then for 1 hr longer and finally submitted to the same work-up procedure as described earlier to yield a yellow oil. Hickman microdistillation of the oil gave 0.2318 g (86%) of LIV [bath temperature 100-105°C (0.05 mm)]: nmr (CCl_4) δ 0.79 and 0.92 (d of d, $J = 6$ Hz, 6H, $7\alpha\text{-CH}_3\text{CHCH}_3$), 1.01 (s, 3H, CH_3) and 3.51 ppm (s, 3H, OCH_3). In a 5 ml round-bottom flask fitted with a magnetic stirrer and maintained under a nitrogen atmosphere, a solution prepared from 0.141 g (0.000630 mole) of LIV, 3 ml of methanol, 1 ml of water and

0.01 g of oxalic acid was stirred at room temperature for 2 hr and 0.25 ml of saturated sodium bicarbonate solution was added. After the solvents were removed in vacuo and the residue was dissolved in ether and water (10 ml each), the organic and aqueous layers were separated, and the aqueous layer was extracted with 3 x 10 ml of ether. The combined ethereal extracts were washed with brine, dried (Na_2SO_4) and concentrated to give an oil which upon Hickman microdistillation yielded 0.1163 g (88%) of LII [bath temperature 103-105°C (0.08 mm)]: ir (film) 3420 (OH), 1733 (C=O), 1458, 1363, 1158 and 1073 cm^{-1} ; nmr (CCl_4) δ 0.83 and 0.88 (d of d, $J = 7$ Hz, 6H, $7\alpha\text{-CH}_3\text{CHCH}_3$) and 1.17 ppm (s, 3H, CH_3); mass spectrum (70eV) m/e 210 (M^+), EMD 210.16188 (calcd: 210.16186).

Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_2$: C, 74.29; H, 10.47. Found: C, 74.01; H, 10.65.

Equilibration of the Isomers of 4-Hydroxy-
4-methyl-7-isopropyl-perhydroindan-1-one

In a 5 ml round-bottom flask fitted with a reflux condenser and a magnetic stirrer and maintained under a nitrogen atmosphere, a solution of 0.050 g of XLVIII in 3 ml of 0.5% methanolic sodium methoxide was refluxed with stirring for 1 hr and was then cooled to room temperature. One drop of saturated sodium bicarbonate solution was added, and the solvent was removed in vacuo. The residue was dissolved in ether and water, and the ether layer was isolated, dried (Na_2SO_4) and concentrated to yield 0.048 g (96%) of XVII. The same procedure applied to 0.050 g of LII left it unchanged, giving complete recovery of starting material. In another experiment, a solution of 0.050 g of LII in 5 ml of anhydrous

tetrahydrofuran and 0.53 g of a 1% t-butyl alcohol solution of potassium t-butoxide (0.20 eq potassium t-butoxide) was refluxed for 12 hr with vigorous stirring. Normal work-up produced only unchanged starting material.

Racemic Oplopanone (XVI)

Following the procedure of Kříž, Beneš and Peška (35), a 25 ml three-neck flask equipped with a mechanical stirrer, a gas dispersion tube and a 25 ml addition funnel, and maintained under a nitrogen atmosphere was charged with 0.095 g of a 53% sodium hydride-oil dispersion, and it was washed with 2 x 10 ml of anhydrous hexane to remove the oil, leaving 0.0540 g (0.00225 mole) of sodium hydride. Five milliliters of anhydrous dimethyl sulfoxide was added and the suspension was warmed with vigorous stirring to 70°C for 30 min during which time a clear solution containing dimethylsodium was formed. The reaction mixture was cooled to room temperature and a steady stream of acetylene was bubbled through it for 30 min to form a clear, black solution of sodium acetylide in dimethylsulfoxide. Maintaining a slow stream of acetylene through the reaction mixture, a solution of 0.158 g (0.000750 mole) of XVII in 5 ml of anhydrous tetrahydrofuran was added dropwise over 30 min, and the mixture was stirred at room temperature overnight. The acetylene flow was discontinued and about 0.1 g of solid ammonium chloride added. The reaction mixture was filtered and the solvents were removed by lyophilization. The residue was dissolved in a mixture of ether and water, and the aqueous layer was isolated and extracted with fresh ether. The combined ethereal extracts were washed with brine, dried (Na_2SO_4) and concentrated to give 0.1512 g of a viscous yellow oil whose nmr (CCl_4) spectrum displayed a one proton

absorption at δ 2.43 ppm, characteristic of an ethynyl proton, and a two proton absorption at δ 3.83 ppm, for the OH protons, which is consistent with the expected ethynyl carbinol structure LVII. In accordance with the procedure of Jacques (36), the 0.1512 g of yellow oil was dissolved in 15 ml of ethyl acetate with 0.30 g of mercuric acetate and stirred at room temperature for 24 hr under a nitrogen atmosphere. With vigorous stirring, hydrogen sulfide was bubbled through the reaction mixture for about 10 min until the black precipate was completely formed. After filtration through celite, all solvents were removed in vacuo to leave 0.090 g of a yellow oil whose nmr (CCl_4) displayed two three-proton absorptions at δ 2.09 and 2.16 ppm, characteristic of acetyl groups, and a one proton absorption at δ 3.28 ppm, for the OH proton, which is consistent with the expected α -acetoxy methyl ketone LVIII. Following a procedure derived from that reported by Chapman (37) for removal of an acetoxy group α to a carbonyl group, in a 25 ml three-neck flask equipped with a Dewar condenser and mechanical stirrer was collected 10 ml of liquid ammonia (freshly distilled from dissolved sodium) and a solution of 0.090 g of the yellow oil in 5 ml anhydrous dioxane was added, followed by about 0.065 g (5 fold excess) of calcium. After stirring at reflux for 1 hr, the blue solution was filtered into a flask containing about 0.1 g solid ammonium chloride and swirled until the blue color disappeared. The solvents were removed in vacuo, and the residue was dissolved in ether and water. The ether layer was isolated, dried (Na_2SO_4) and concentrated to give 0.0561 g of a light yellow oil which was dissolved in 5 ml of acetone and titrated with Jones reagent (57) until the color of the reagent persisted. One drop of isopropyl

alcohol was added, and the reaction mixture was filtered. The removal of all solvents in vacuo left a yellow oil (0.050 g), which was chromatographed on 5 g of silica gel. Elution with 40% ether in hexane gave 0.015 g (8.4% from XVII) of oplopanone XVI: mp 101.5-102°C; nmr (CDCl_3) δ 0.69 and 0.89 (d of d, $J = 6$ Hz, 6H, CH_3CHCH_3), 1.19 (s, 3H, CH_3) and 2.18 ppm (s, 3H, Ac); ir (CCl_4) 3583 (OH), 1711 (C=O), 1466, 1385, 1370 and 1359 cm^{-1} .

Attempted Dehydration of 7-Acetoxy-2-hydroxy-3-methoxy-7-methyl-4 β -isopropyl-2,4,5,6,7,7a-hexahydroindene (XLIX)

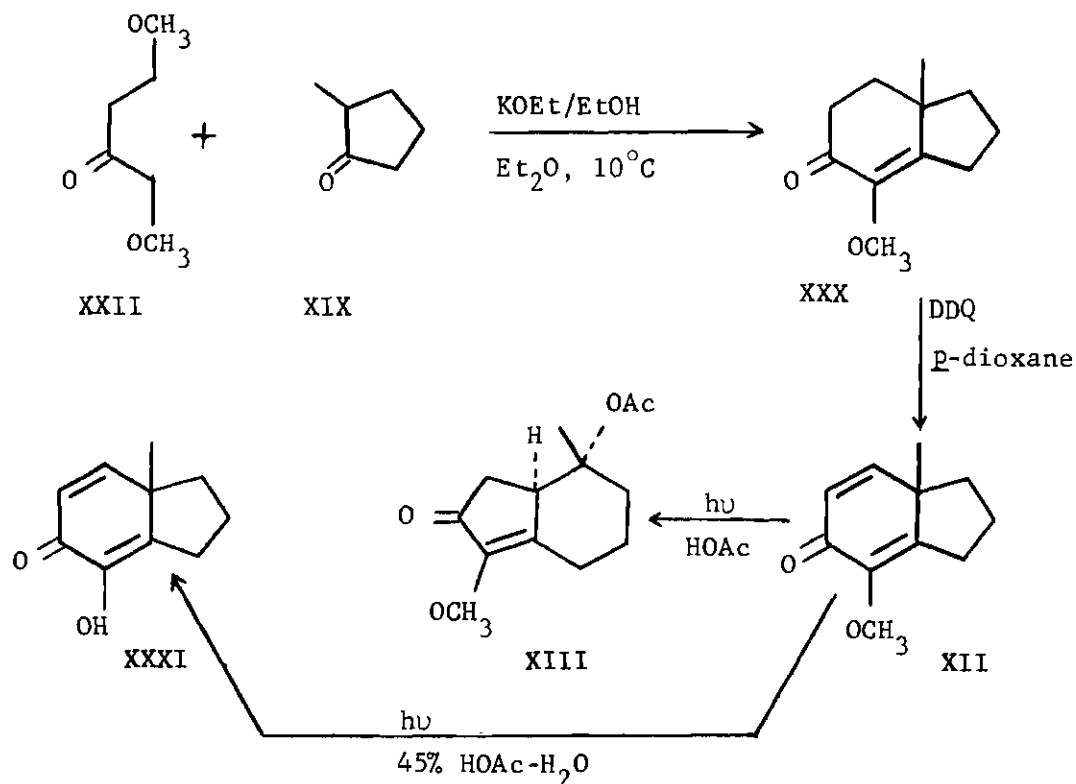
In a 25 ml round-bottom flask fitted with a magnetic stirrer and maintained under a nitrogen atmosphere was placed 0.12 g (0.00050 mole) XLIX in 5 ml of dry acetonitrile and the solution was cooled to 0°C using an ice bath. A solution of 0.250 g (0.00105 mole) of (carboxysulfamoyl) triethyl ammonium hydroxide inner salt, methyl ester (55) in 10 ml of dry acetonitrile was added dropwise over one half hour. After addition was complete, the reaction mixture was warmed to room temperature and stirred for 3 hr. The solvent was removed in vacuo at room temperature and the residue was dissolved in ether and water (10 ml each). The ether layer was isolated, washed with water, dried (Na_2SO_4) and concentrated to give 0.100 g of a brown oil which could not be identified by nmr or ir analysis.

CHAPTER IV

DISCUSSION OF RESULTS

As discussed in Chapter I, the first part of the research described herein was the synthesis and photolysis of dienone XII to determine if, indeed, the previous examples of C-4 electron releasing substituents causing the photolysis of 6/5-fused cyclohexadienones to give the same type photoproducts as 6/6-fused cyclohexadienones would hold true for a C-4 methoxyl substituent. The synthesis of dienone XII was executed in a manner similar to the synthesis of its 6/6-fused analogue XIV (14).

Chart 4



Synthesis and Photolysis of 4-Methoxydienones

Using a modification of the procedure of Wenkert (18b), as shown in Chart 4, 1,4-dimethoxy-2-butanone (XXII) was condensed with 2-methylcyclopentanone (XXIX) to give the enone XXX. The butanone XXII was readily prepared in two steps from 2-butyne-1,4-diol following the method of Hennion and Kupiecki (29), while the cyclopentanone XXIX was either purchased commercially or prepared (39) from 2-carbethoxycyclopentanone (39). The base catalysed condensation at 10°C followed by stirring at room temperature for three hours caused the elimination of methanol from XXII to give 1-methoxy-3-buten-2-one. This then underwent Michael type condensation with XXIX, and the resulting methoxy diketone was cyclized by a Claisen type condensation to the enone XXX. Simple vacuum distillation of the crude reaction product gave pure enone XXX with no indication of the presence of any of the intermediate ketol, which was an isolated intermediate in the 6/6-fused analogue case. Oxidation of the enone XXX to the dienone XII proceeded smoothly using 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) in refluxing p-dioxane according to the procedure of Burn, Kirk and Petrow (30) to give 60 percent conversion and a 51 percent yield based on unrecovered enone. Using DDQ in refluxing benzene with glacial acetic acid gave only 40 percent conversion to the dienone, while oxidation of the enone XXX using selenium dioxide in anhydrous t-butyl alcohol with glacial acetic acid gave complete conversion to the dienone but in only a 35 percent yield. The spectral and analytical data for enone XXX and dienone XII were all consistent with the assigned structures. Of interest, however, are the ultraviolet spectra of these compounds [λ_{max} 254 nm (ϵ 8,260) for XXX and 242 nm (ϵ 5,430) for XII] which show significantly lower molar extinction coefficients than do their C-4 methyl

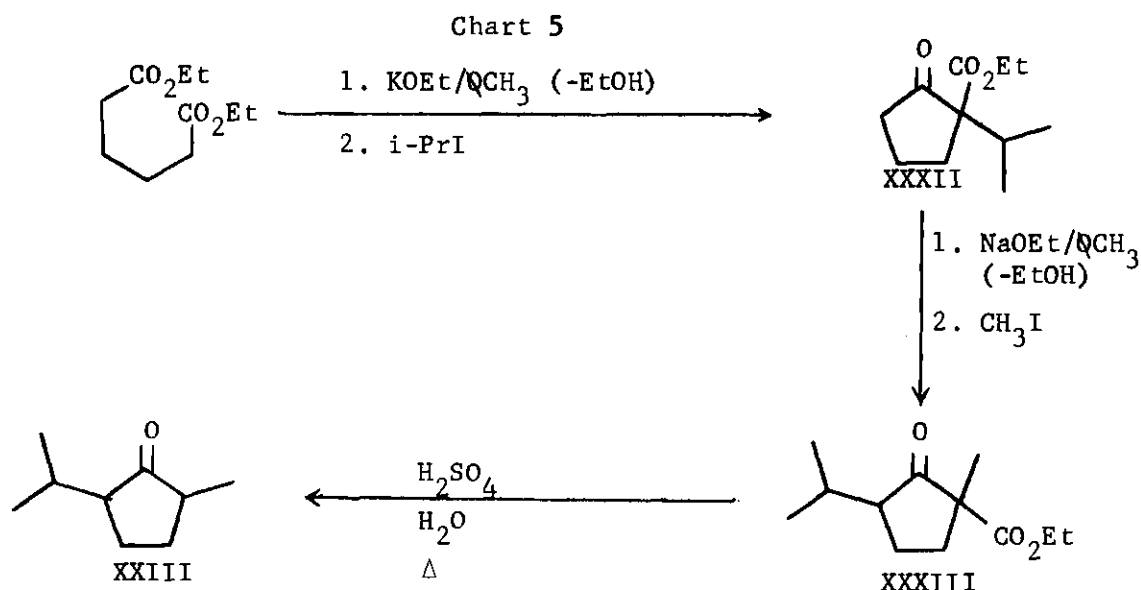
analogues [λ_{max} 245 nm (ϵ 13,700) and 243 nm (ϵ 11,900) respectively (10)].

This variance in molar extinction coefficient is similar to that noted by Reusch (40a,b) in his work with α -methoxy enones in steroidal systems.

The irradiation of dienone XII in glacial acetic acid for four hours with a Hanovia 450-watt high pressure lamp with a Pyrex probe gave a smooth conversion into the 5/6-fused acetoxo ketone photoproduct XIII. A single compound was formed in 85 percent yield and its spectral and analytical properties were consistent with the assigned structure XIII. Tricyclic compounds analogous to X were not detected. As with the 6/6-fused analogue system, glacial acetic acid was necessary instead of aqueous acetic acid since irradiation of XII in the latter solvent yielded only the hydrolyzed dienone XXXI. The hydrolysis is apparently light induced since dienone XII is stable to aqueous acetic acid for four hours at 25-30°C in the absence of light. The nmr spectrum of XIII showed a doublet at δ 3.08 ppm ($J = 4$ Hz, 1H) at both 60 MHz and 100 MHz. In decoupling experiments at 100 MHz, irradiation of the doublet resulted in the collapse of the triplet to a singlet, while irradiation of the triplet resulted in the doublet collapsing to a singlet. This absorption pattern was attributed to the two C-1 methylene protons and the one C-7a proton forming an AB₂ system (41). It is interesting that the C-1 methylene protons, which appear to be in quite different environments, are actually magnetically identical. This same general pattern and position of absorption has been observed in the 5/6-fused photoproducts from the unsubstituted and the methyl substituted dienone (10) as well as for the 5/7-fused hydroxy ketones of the type V (see Chart 1) from the 6/6-fused dienone systems (8). The nmr absorption of the C-7 methyl group, 1.28 ppm,

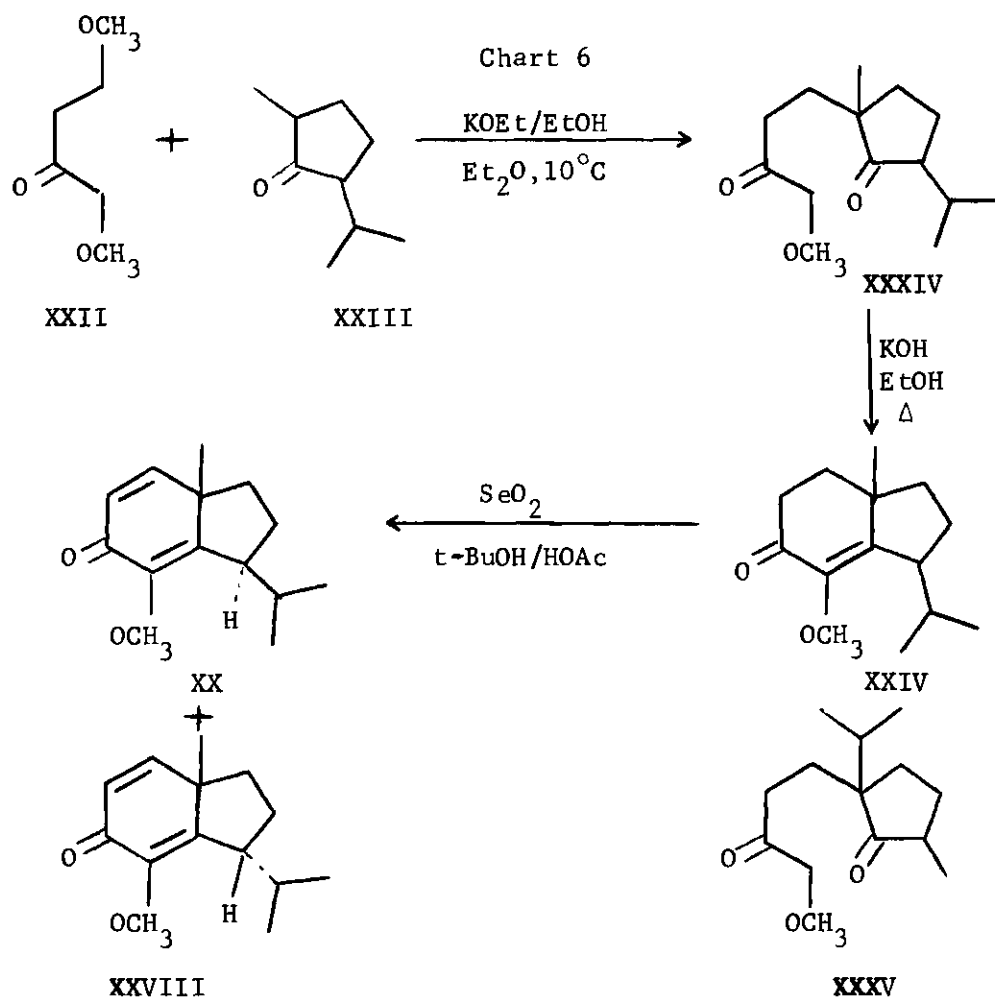
occurs at higher field than would be expected for a methyl group attached to a tertiary carbon bearing an acetoxyl function (in the nmr spectrum of t-butyl acetate the methyl absorption occurs at 1.45 ppm). This indicates that it is axially β -oriented and thus shielded by the Δ^3 double bond. This same phenomenon occurs in the 5/7-fused photoproducts of the type V. Therefore, from the analogy of the nmr spectra as well as the proposed mechanisms of formation for the 5/6-fused and the 5/7-fused photoproducts, the stereochemistry of XIII can be assigned as shown at C-7 and C-7a based on the known structures of type V photoproducts.

With the knowledge that a C-4 methoxy substituent did indeed influence the photochemical rearrangement of a 6/5-fused cyclohexadienone to produce a high yield of 5/6-fused acetoxo ketone photoproducts of the type VIII (see Chart 2), the use of such a photolysis in the synthesis of oplopanone (XVI) seemed even more attractive and the second phase of the research described here was begun, the synthesis of racemic oplopanone. The proposed starting material for the synthesis, 2-methyl-5-isopropylcyclopentanone (XXIII) had been synthesized by many methods, but they all seemed either unnecessarily long (20,32) or relatively expensive (42,43). Therefore, a three step method starting with diethyl adipate was developed using a Dieckmann type cyclization scheme described by Sisido (33) as shown in Chart 5. Cyclization of diethyl adipate with potassium ethoxide while removing the ethanol by azeotropic distillation with toluene gave the potassium enolate of 2-carbethoxycyclopentanone, which was treated with isopropyl iodide to give XXXII. Treatment of XXXII with sodium ethoxide and azeotropic removal of ethanol led to the formation of the sodium enolate of 2-carbethoxy-5-isopropylcyclopentanone



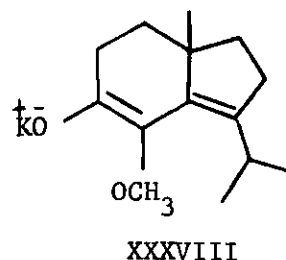
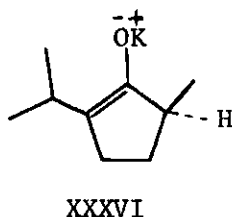
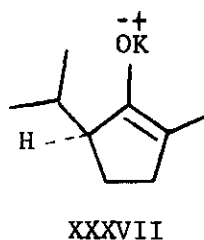
via diethyl-2-isopropyl adipate. This enolate was then reacted with methyl iodide to give XXXIII. Acid hydrolysis of XXXIII and decarboxylation with gentle heating gave a good yield of XXIII.

As in the synthesis of enone XXX, the condensation of XXII and XXIII was carried out according to the procedure of Wenkert (18b) as shown in Chart 6. In using an unsymmetrical ketone such as XXIII in a Michael type condensation the possibility of the reaction occurring at both the α and α' positions must be considered. Therefore, condensation of XXII and XXIII could occur either at C-2 to give the tertiary methyl compound XXXIV or at C-5 to give the tertiary isopropyl isomer XXXV. Comparison of the potassium enolates necessary for the condensation shows that the $A^{1,2}$ -strain (21) between the solvated oxygen anion and the isopropyl group in enolate XXXVI, which would lead to formation of



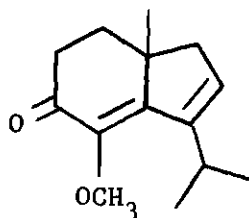
XXXV, should be greater than the $A^{1,2}$ -strain between the solvated oxygen anion and the methyl group in enolate XXXVII, which would lead to formation of XXXIV. Under equilibrating conditions, enolate XXXVII should be preferred, and, therefore, this enolate should participate in the Michael reaction (44). This was found to be true in the exclusive formation of the methoxy diketone XXXIV from the base catalysed condensation of XXII and XXIII at 10°C followed by stirring at room temperature for three hours. Compound XXXIV was shown by glc and nmr analysis to be a mixture of cis and trans isomers. It is interesting that these reaction conditions did

not lead to the formation of the enone XXIV or its ketol precursor. Treatment of this mixture of isomers of XXXIV with alcoholic potassium hydroxide at reflux for one hr effected cyclization to pure XXIV in 63 percent yield.



From the discussion presented in Chapter I concerning the expected relative stabilities of the β -oriented isopropyl enone XXIV and the α -oriented isopropyl enone XXVII, it was assumed that the single enone formed had the structure XXIV and that an insufficient amount of the enone XXVII had been formed to detect (i.e. <1 percent). To confirm this, it was felt that if the linearly conjugated enolate anion of the enone (XXXVIII) were prepared, kinetic protonation of it would result in the addition of the proton from the bottom side of the molecule to avoid a 1,3-interaction of the proton donor with the axial angular methyl group. Thus protonation of XXVIII would be expected to give rise to XXIV. Therefore, the enone product was treated with three equivalents of potassium t-butoxide in t-butyl alcohol with heating to form the enolate XXXVIII which was then rapidly protonated with three equivalents of glacial acetic acid. Rapid but careful workup gave complete recovery of a single compound which was identical by nmr, ir and glc analysis to the

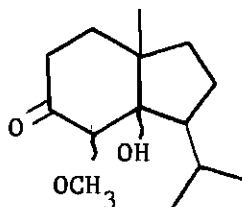
starting enone. This corroborated the theoretical argument presented in Chapter I and established the structure **XXIV** as the correct assignment for the single enone product.



XXXIX

Oxidation of **XXIV** with DDQ using the procedure of Burn, Kirk and Petrow (30) gave a 43 percent yield of a compound that was assigned the linearly conjugated dienone structure **XXXIX** based on its nmr spectral properties. Only a 5 percent yield of the desired cross-conjugated dienone **XX** was obtained. Using a modification of the procedure of Bernstein (31), treatment of **XXIV** with selenium dioxide in t-butyl alcohol led to a 75 percent conversion into the cross-conjugated dienone with no sign of the linearly conjugated isomer. This difference in the action of the two reagents probably arises in the difference in their respective mechanisms of reaction. The proposed mechanism for DDQ oxidation (45) requires the formation of the enol and subsequent hydride abstraction by the DDQ molecule to give the enone system, whereas in selenium dioxide oxidation coordination of the selenium with the carbonyl oxygen yields a postulated intermediate selenite ester that decomposes to the desired enone system. For compound **XXIV** the more highly substituted linearly conjugated enol must be more readily formed than the homoannular enol so that DDQ oxidation forms the linearly conjugated dienone, while

selenium dioxide, not depending upon a prior enolization reaction, gives rise to the desired cross-conjugated dienone.

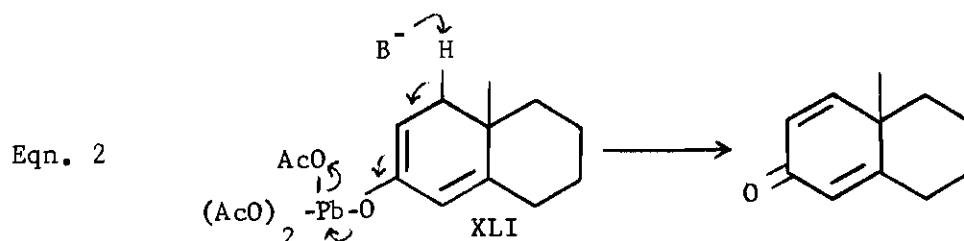


XL

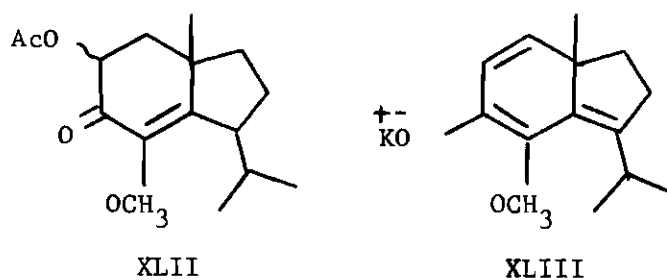
It was important that only freshly prepared and sublimed selenium dioxide be used in the oxidation of **XXIV**. When commercially obtained selenium dioxide was used, a new compound was formed in varying yields depending on the quality of the selenium dioxide. This new compound showed the following spectral properties: ir (film) 3480, 1733 and 1648 cm^{-1} ; nmr (CCl_4) δ 0.83 and 0.88 (d of d, $J = 7$ Hz, 6H), 0.93 (s, 3H) and 3.34 ppm (s, 3H); mass spectrum (70eV) m/e 240. These data are consistent with the ketol structure **XL**, which could result from simple, 1,4-addition of water to the enone **XXIV**. However, treatment of the new compound with ethanolic potassium hydroxide, conditions identical to the synthesis of **XXIV**, failed to convert it into **XXIV**, and the cyclization of **XXXIV** to **XXIV** must proceed via a ketol of the type **XL**. It could be that isomeric ketols are involved, one of which is sterically able to dehydrate while the other is not. No further work was done to elucidate the structure of this compound, since by careful work the formation of this compound could be avoided in the selenium dioxide oxidation.

From work done previously in these laboratories by Dawson (47), it was known that oxidations of enone systems with lead tetraacetate often led to cross-conjugated dienone systems. The proposed mechanism

required the formation of a plumbic ester such as XLI and its subsequent base catalysed decomposition as shown in equation 2. Presumably the



base involved was the acetate anion. In an attempt to use this reaction in the synthesis of XX, the procedure of Seebach (48) was followed to react XXIV with lead tetraacetate, except that an equivalent of sodium acetate was added, hopefully to catalyze the desired elimination reaction. However, only 30 percent of the starting material reacted and all of that was converted smoothly into the α -acetoxyl compound XLII. The formation of the desired dienone XX did not take place.

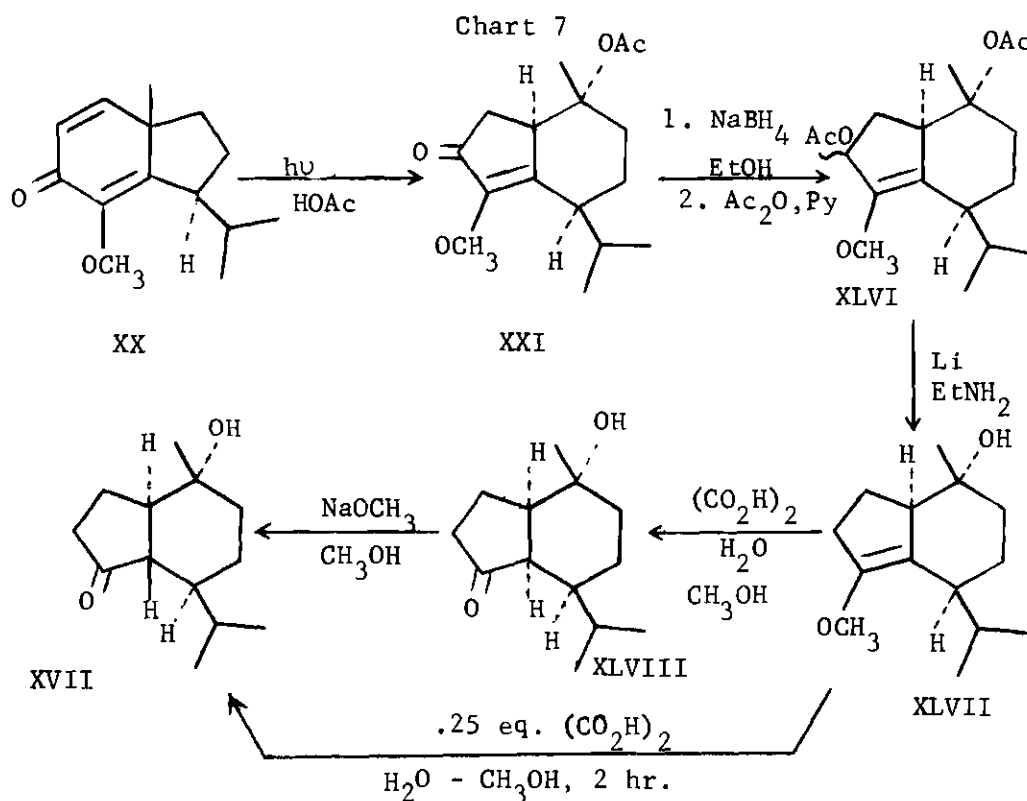


In all cases where oxidation of XXIV led to formation of the cross-conjugated dienone, it was found that the dienone product existed as a mixture of two isomers in the ratio of 5 to 1. Attempted equilibration of this mixture by refluxing it with a catalytic amount of potassium

t-butoxide in t-butyl alcohol did not lead to any detectable change in its composition; thus, this 5 to 1 ratio of the isomers appears to be the equilibrium composition. From the discussion presented in Chapter I this equilibrium mixture should contain 5 parts of the β -oriented isopropyl isomer XX to 1 part of the α -isopropyl isomer XXVIII. Following the procedure of Shapiro (34) for making the conjugate enolate of α -methoxy cross-conjugated dienones, the 5 to 1 mixture of XX and XXVIII was reacted with 10 equivalents of potassium t-butoxide in dimethyl sulfoxide in an attempt to make the conjugated enolate XLIII. Kinetic protonation of XLIII should proceed with the proton entering from the bottom side of the molecule opposite the axial methyl group and give mainly XX as the product. However, only an unidentifiable oil was obtained from the reaction, the nmr spectrum of which showed no methoxyl groups, and no helpful information was gained from this experiment. Since the isopropyl group and the methyl group are sterically close enough to interact magnetically in the β -isopropyl isomer (XX) but not in the α -isopropyl isomer (XXVIII), it was thought that the two isomers could be differentiated using nmr analysis. The β -isomer might be expected to show a Nuclear Overhauser Effect (49,50) in the absorption of the isopropyl group if the methyl group absorption were irradiated, while the α -isomer should not show any such effect. Unfortunately, with the instrumentation available in these laboratories, it was impossible to make such a determination when the groups involved had such close nmr absorptions. The positive evidence that the major isomer was indeed the β -oriented isopropyl isomer XX was obtained from the subsequent transformations which were used to convert this isomer into the naturally

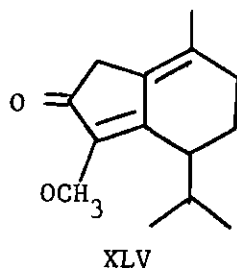
occurring compound oplopanone (XVI) which was known to have a β -oriented isopropyl group (15a).

The mixture of dienone isomers could be separated into its pure components by careful chromatography on a silica gel column. However, it was found to be much simpler to carry out the irradiation on the mixture and then separate the α - and β -isopropyl isomers of the photo-products by fractional crystallization from a hexane-ether solvent.



Synthesis of β -Isopropyl Hydroxy Ketone Series

Irradiation of the 5 to 1 mixture of **XX** and **XXVIII** in glacial acetic acid with a Hanovia 450-watt high pressure lamp for four hours with a Pyrex probe gave smooth conversion into a 5 to 1 mixture of the 5/6-fused acetoxy ketone photoproducts **XXI** and **XLIV**. To prove that no epimerization of the isopropyl group occurred during photolysis, a sample of pure **XX** was irradiated under the same conditions, as shown in Chart 7, and was transformed in 91 percent yield into a single photoproduct **XXI**, which was identical to the major isomer formed in the irradiation of the dienone mixture. Molecular models of **XXI** and **XLIV** constructed from Dreiding Stereomodels show that structure **XXI** with the β -isopropyl group should be greatly favored over structure **XLIV** with the α -isopropyl group since in **XLIV** either the isopropyl group or the five-membered ring has to be located axially to the six-membered ring when it is in a chair form, while in **XXI** all groups can be equatorial when the six-membered ring is in a chair form. In efforts to verify the structural assignments made for the acetoxy ketone photoproducts, the mixture of the two isomers was treated under various epimerizing conditions to convert the mixture into the more stable β -isopropyl isomer **XXI**. However, treatment of the mixture with both acidic (trifluoroacetic acid-carbon tetrachloride) and basic (sodium deuterium oxide) reagents led either to no detectable change by nmr analysis under very mild conditions or to elimination of acetic acid to form the linear dienone **XLV** under slightly more severe



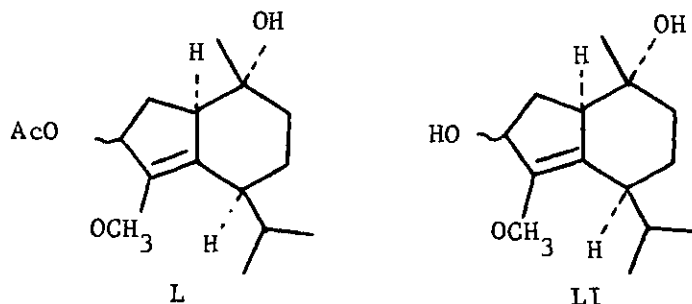
conditions. No intermediate conditions could be found that would allow epimerization of the isopropyl group without elimination of acetic acid. This probably arises from the fact that when the isopropyl group is α -oriented, and thus susceptible to epimerization, the C-4 proton that must be removed to effect isopropyl epimerization has an equatorial configuration so that the axial C-7a proton is much more easily removed forming the homoannular conjugate enolate, which leads to elimination of acetic acid.

The stereochemistry of XXI and XLIV at C-7 and C-7a was assigned based on the correlation of their nmr spectra with that of the model photoproduct XIII. In XXI the two C-1 methylene protons and one C-7a proton formed an AB₂ system giving a doublet at δ 2.18 ppm ($J = 4.5$ Hz, 2H) and a triplet at δ 3.01 ppm ($J = 4.5$ Hz, 1H) respectively, while in XLIV this same AB₂ system gave a doublet at δ 2.30 ppm ($J = 4$ Hz, 2H) and a triplet at δ 3.21 ppm ($J = 4$ Hz, 1H). As in the photoproduct XIII, the C-7 methyl groups in both XXI and XLIV show higher nmr absorption, δ 1.22 and 1.28 ppm, respectively, than would be expected based on an absorption of δ 1.45 ppm for *t*-butyl acetate. This indicates that the methyl groups are axially β -oriented and thus shielded by the Δ^3 double bond. The nmr absorptions of the isopropyl groups in XXI and XLIV were somewhat deceiving since the doublet of doublets for the β -isopropyl group in XXI, δ 0.88 and 0.97 ppm ($J = 6$ Hz), overlapped to form an apparent triplet in a 60 MHz spectrum, while the doublet of doublets for the α -isopropyl group in XLIV, δ 0.84 and 1.02 ($J = 6$ Hz), were well separated. In the naturally occurring oplopanone (XVI), as well as in its degradation product XVII, both of which are known to have β -oriented

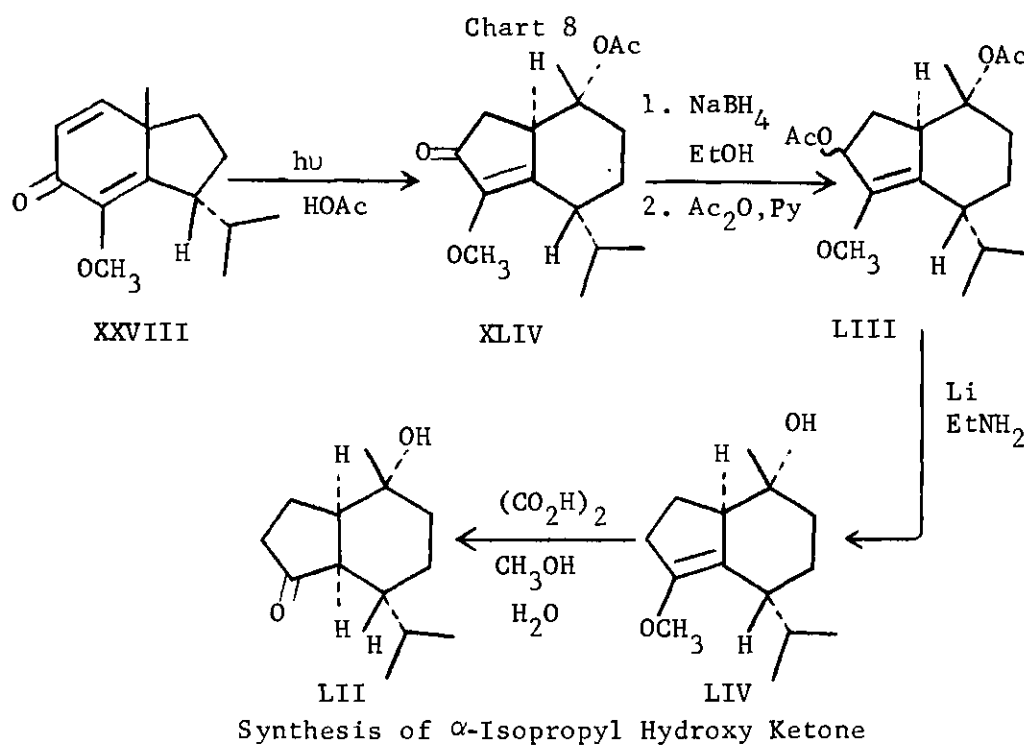
isopropyl groups, the nmr absorptions show well separated doublets of doublets (15a).

The removal of the carbonyl function of XXI was accomplished by using the procedure reported by Ireland (51) and by Caine and Dawson (47,52) as shown in Chart 7. Treatment of XXI with sodium borohydride in ethanol gave smooth reduction of the carbonyl function to the desired allylic alcohol, which was stirred with acetic anhydride in pyridine to form the diacetoxyl compound XLVI in 94 percent yield. The diacetoxyl product was formed as a 2 to 1 mixture of two isomers differing only in the stereochemistry of the allylic acetoxyl groups. The mixture of isomers was purified by crystallization from hexane at -78°C , but upon warming to room temperature became a viscous oil. The isomeric mixture of XLVI was dissolved in ether and ethylamine at -78°C and excess lithium was dissolved in the solution until the blue coloration of solvated electrons persisted for an hour. This resulted in the dual reaction of the reduction of the tertiary acetoxyl group plus the removal of the allylic acetoxyl group to give the hydroxy enol ether XLVII. It was found that the lithium-ethylamine reduction proceeded in higher yield if an equivalent of *t*-butyl alcohol were added with the mixture of XLVI to serve as a proton donor. The proton donor prevented the concentration of lithium ethyl amide from building up. In runs in which no proton donor was used a side reaction, probably involving cleavage of the allylic acetoxyl group by lithium ethyl amide, led to the production of alcohol XLIX. In an attempt to prepare the hydroxy allyl acetate L, which could serve as an internal proton donor in the lithium-ethylamine reduction,

compound XXI was reduced with 2 equivalents of lithium aluminum hydride in ether and the resulting diol LI was reacted with acetic anhydride in pyridine. Only polymerization resulted and the desired L was not detected.

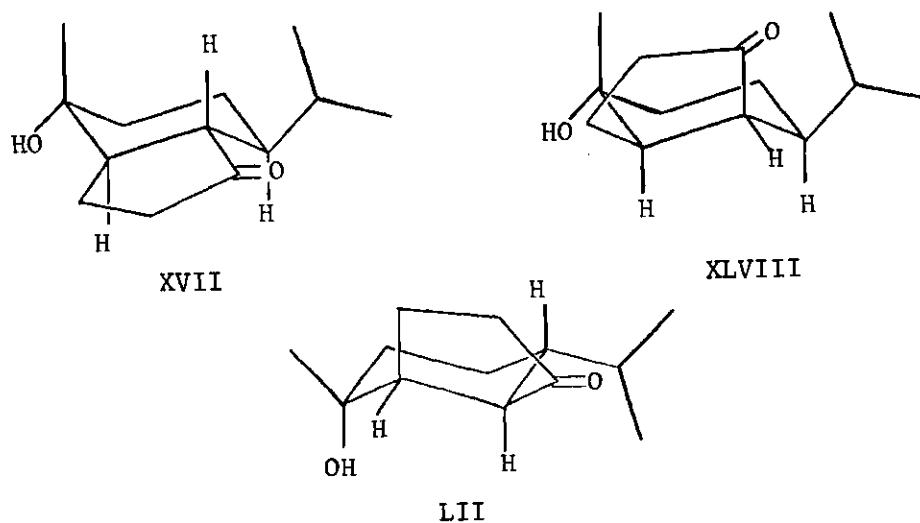


The hydrolysis of the enol ether XLVII in aqueous methanol using 0.25 eq of oxalic acid for two hours gave good conversion into the hydroxy ketone XVII which showed the same absorptions in nmr and ir analysis as those reported for the degradation compound of the same structure from natural oplopanone by Minato (15a,b). The synthetic compound XVII was stable to treatment by 0.5 percent sodium methoxide in refluxing methanol, which indicated that it had the more stable trans-fused ring system. Alternatively, the hydrolysis of XLVII using only a catalytic amount of oxalic acid and letting the reaction stir for one-half hour resulted in the kinetic addition of the angular proton, opposite to the axial C-7 methyl group, to give the cis-fused hydroxy ketone XLVIII. Treatment of XLVIII with 0.5 percent sodium methoxide in refluxing methanol led to its rapid epimerization to the trans-fused hydroxy ketone XVII. After being allowed to stand in an ether solution for several days, a sample of XLVIII was found to have undergone partial epimerization to XVII.



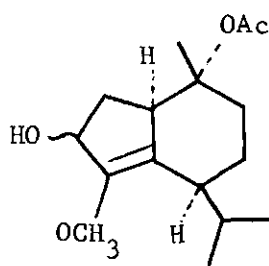
To help confirm the assigned stereochemistry of hydroxy ketones XVII and XLVIII, the α -isopropyl isomer LII was prepared from the α -isopropyl photoproduct (XLVI) as shown in Chart 8. As before, treatment of XLIV with sodium borohydride in ethanol gave the allylic alcohol, which was stirred with acetic anhydride in pyridine to give the diacetoxyl compound LIII. Crystallization from hexane-ether at -20°C afforded LIII as a mixture of isomers of the acetoxyl group. Reduction of LIII by lithium in ethylamine using *t*-butyl alcohol as a proton donor and following the procedure described earlier removed the allyl acetoxyl group and reduced the tertiary acetoxyl group to give the hydroxy enol either LIV. Hydrolysis of LIV in aqueous methanol with oxalic acid

produced the hydroxy ketone LII. Treatment of LII with 0.5 percent sodium methoxide in refluxing methanol left it unchanged by nmr and ir analysis, as did treatment with 0.2 eq of potassium t-butoxide in refluxing tetrahydrofuran, which indicated that it had the more stable cis-fused ring system. As would be expected, the trans-fused system was so sterically unfavorable that it could not be formed from either kinetic or equilibrium controlled hydrolysis. The finding that hydrolysis of XLVII could give rise to two isomeric hydroxy ketones while hydrolysis of LIV could give only one provides further evidence for the structural assignments of these enol ethers.

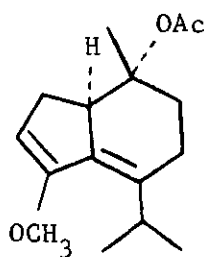


The three hydroxy ketone isomers XVII, XLVIII and LII could easily be differentiated by ir and nmr analysis. Especially different were the nmr absorptions for the isopropyl and methyl groups. For compound XVII the isopropyl group appears as a well separated doublet of doublets at δ 0.77 and 0.92 ppm ($J = 6$ Hz) and the methyl group as a singlet at δ 1.14 ppm, which is due to the close proximity of the carbonyl and isopropyl groups, while in XLVIII the axial carbonyl and equatorial

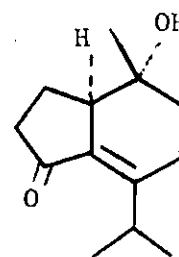
isopropyl groups are separated but the methyl and carbonyl are very close, with the result that the isopropyl group shows a barely distinguishable doublet of doublets at δ 0.88 and 0.90 ppm ($J = 7$ Hz) and the methyl group singlet is rather high field at δ 0.96 ppm. In the α -isopropyl isomer LII, the carbonyl group interacts only slightly with the isopropyl group so that it shows a close doublet of doublets at δ 0.83 and 0.88 ppm ($J = 7$ Hz) and the methyl group singlet is at δ 1.17 ppm.



XLIX



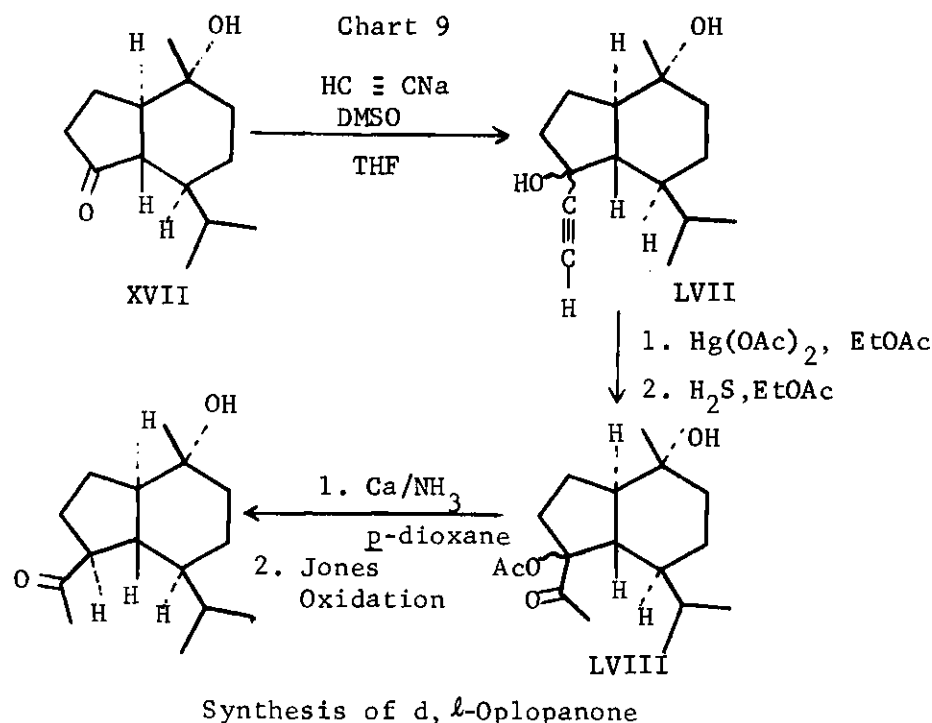
LV



LVI

In a final attempt to prove conclusively the stereochemistry in the hydroxy ketone series (XVII, XLVIII and LII), the allylic alcohol XLIX, from the reduction of the photoproduct XXI, was treated under dehydrating conditions in an effort to prepare the diene LV, which on hydrolysis should give the hydroxy enone LVI. Catalytic hydrogenation of LVI should result in the addition of hydrogen to the double bond from the bottom side opposite to the axially oriented methyl group to give an hydroxy ketone identical to XLVIII which could then be epimerized to an hydroxy ketone identical to XVII. However, attempted dehydration using thionyl chloride in pyridine (53), tosyl chloride in pyridine (54) or (carboxysulfamoyl) triethylammonium hydroxide inner salt, methyl

ester, in acetonitrile (55), all gave only unidentifiable polymers and the desired diene could not be detected.



The conversion of hydroxy ketone XVII into racemic oplopanone (XVI) was accomplished by a series of reactions as shown in Chart 9 which were monitored by ir and nmr analysis, but the intermediates were not isolated and completely characterized. Compound XVII was allowed to react with sodium acetylide in dimethyl sulfoxide and tetrahydrofuran, according to the procedure of Kříž, Beneš and Peška (35), to give the ethynyl carbinol addition product LVII, which showed an nmr absorption at δ 2.43 ppm for the ethynyl proton. The crude LVII was then hydrolyzed with mercuric acetate in ethyl acetate, following the procedure of

Jacques (36) to give the α -acetoxy ketone LVIII which showed nmr absorptions at δ 2.09 and 2.16 ppm for the acetyl and acetoxyl groups. A mechanism for this conversion has been proposed by Fieser (56), but probably the rearrangement involves much simpler intermediates. The α -acetoxyl group was removed by reduction with calcium in ammonia and p-dioxane according to the procedure of Chapman (37), which also led to reduction of the ketone function; oxidation of the secondary alcohol with Jones' reagent (57) in acetone afforded racemic oplopanone. Recrystallization of the synthetic oplopanone from hexane-ether gave a pure sample mp 101.5 - 102°C which was identical to a sample from the natural source by ir, nmr and glc analysis.

The synthetic work reported herein does not conclusively establish the stereochemistry of the acetyl side chain in oplopanone. However, from a study of stereomodels, it appears that non-bonded interactions are minimized when the acetyl side chain is in the β -configuration. Thus the β -isomer should be more thermodynamically stable than the α one. In the reductive removal of the α -acetoxyl group from compound LVIII, the protonation of the resulting calcium enolate should proceed from the side of the molecule opposite the β -oriented axial methyl group and the axial angular hydrogen atom, thus leading to the β -oriented acetyl side chain as the kinetic product. Therefore, since a β -acetyl side chain should be preferred both kinetically and thermodynamically in this system, the original proposal for the stereochemistry at C-3 by Minato (15) is probably correct.

CHAPTER V

CONCLUSIONS

The 6/5-fused cross-conjugated cyclohexadienone with a C-4 methoxyl substituent, XII, was prepared and shown to rearrange to the acetoxy ketone XIII upon irradiation in acetic acid. This was another example of the manner in which a C-4 electron donating substituent influences the photochemical rearrangement of a 6/5-fused cyclohexadienone to form a 5/6-fused photoproduct.

The related 6/5-fused cross-conjugated cyclohexadienone with a β -oriented isopropyl side chain XX was prepared and its photochemistry studied. The 5/6-fused acetoxy ketone photoproduct XXI was converted by a series of reactions into racemic oplopanone (XVI) which was identical by nmr, ir and glc analysis to a sample of the naturally occurring compound.

The conversion of the photoproduct XXI into racemic oplopanone (XVI) using standard reactions which predictably affected the stereochemical integrity of the molecule constituted a proof of structure of the photoproduct XXI since the structure of oplopanone (XVI) was already established. The structures assigned to photoproducts XIII and XLIV were confirmed by their chemical and spectral correlation with compound XXI.

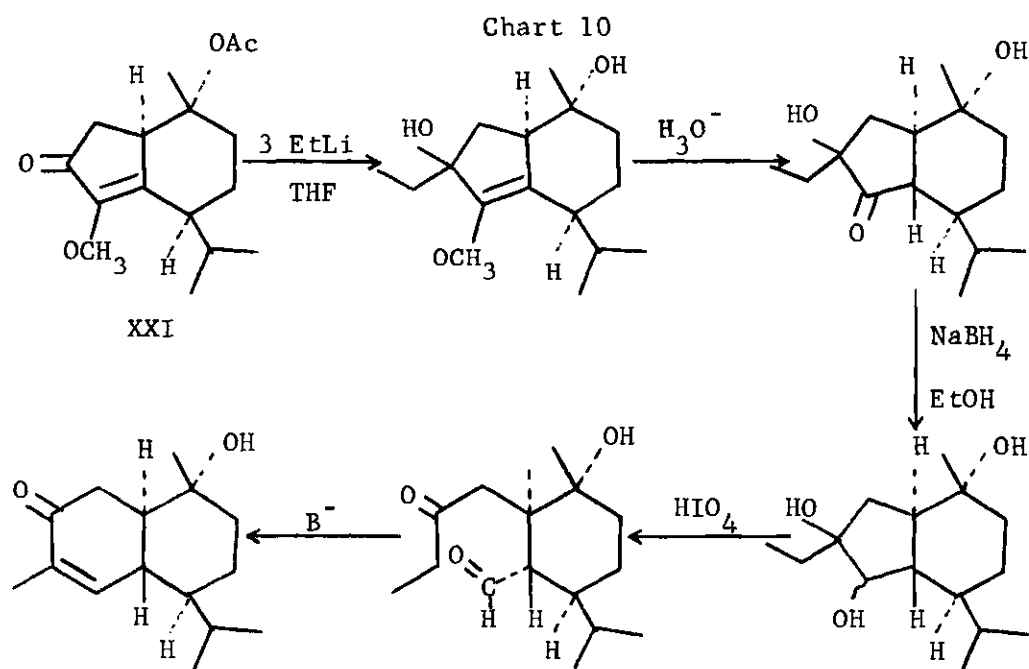
Compound XXI appears to be a potentially useful intermediate for the total synthesis of other known hydroxy ketone sesquiterpenes such as members of the α -cadinol (XVIII) family (16a,b). Thus, the present work

involving the development of the synthesis and proof of structure of **XXI** provides a foundation for further advances in natural products total synthesis.

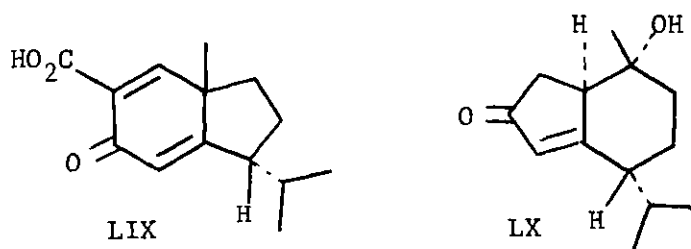
CHAPTER VI

RECOMMENDATIONS

Studies should be made to find methods to expand the five-membered ring of the 5/6-fused photoketones so these photoproducts can be used as intermediates in the total syntheses of 6/6-fused bicyclic sesquiterpenes. In particular the five-membered ring of compound **XXI** should be expanded to provide a total synthesis of the sesquiterpene α -cadinol (**XVIII**) (16a,b). A possible pathway is shown in Chart 10.



The effect of other substituents on the cyclohexadienone chromophore should be studied to further correlate the photochemical rearrangement of the 6/6-fused and the 6/5-fused cyclohexadienones. In particular, the effect of an electron withdrawing substituent at C-2 should be studied to determine if the same pattern is observed as with a C-4 electron donating substituent. If indeed the same influence is observed, the 6/5-fused dienone LIX should be prepared which, according to the studies of Levisalles (19), should have an α -oriented isopropyl side chain. The photochemistry of LIX should be studied as a method of preparing the hydroxy ketone LX. Compound LX should serve as an important intermediate in the total synthesis of the sesquiterpene T-murrolol (XIX) (17a,b).



For further confirmation of the structures assigned to photo-product XXI and to oplopanone (XVI), the x-ray crystallographic analysis of one of them should be determined.

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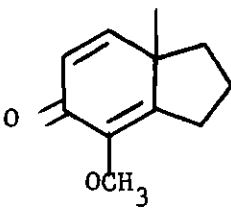
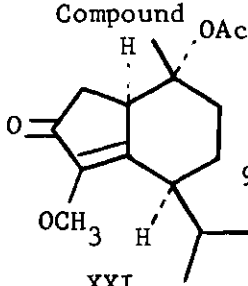
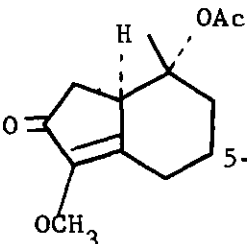
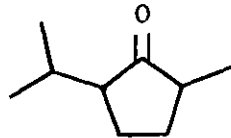
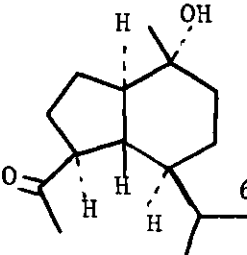
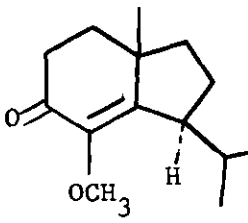
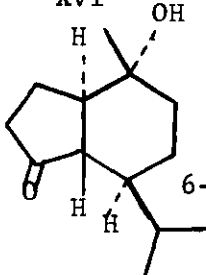
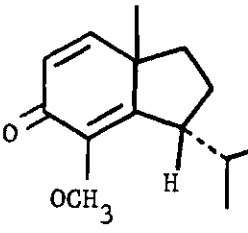
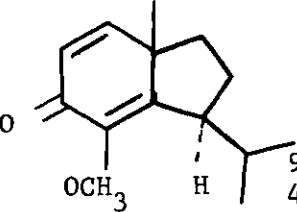
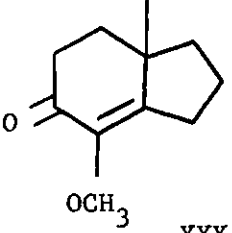
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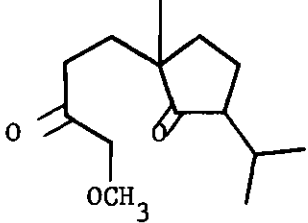
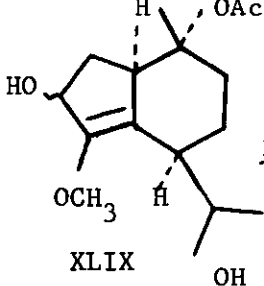
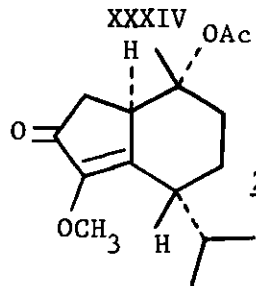
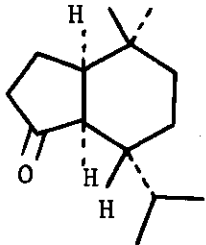
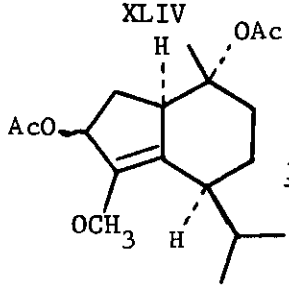
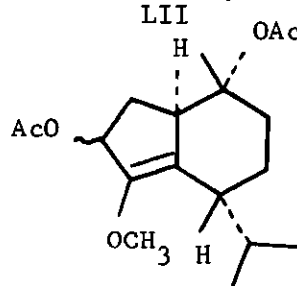
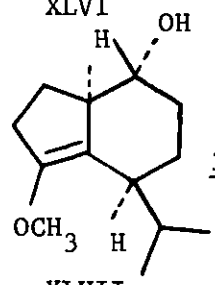
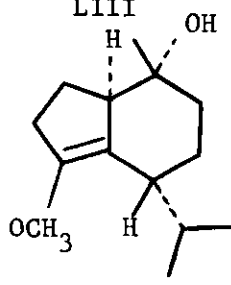
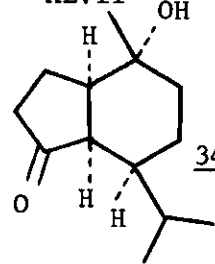
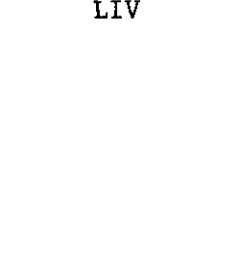
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APPENDIX

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